Stereoselective Synthesis of Pyrrolidinones *via* Nitro-Mannich Reaction

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Towards the Synthesis of Popolohuanone E

A Thesis Presented by

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In Part Fulfilment of the Requirement for

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I, Lisa Rebecca Horsfall confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed……

Date……

Abstract

Part 1: The first section of this thesis details the stereoselective synthesis of pyrrolidinones *via* the nitro-Mannich reaction. Expanding on previous work within the Anderson group, conjugate addition of a diorganozinc species to nitroacrylate **141** was carried out successfully. Subsequent *in situ* nitro-Mannich reaction was then followed by spontaneous lactamisation to afford the desired five-membered ring pyrrolidinone structure.

The reaction was performed in one pot, generating three contiguous stereocentres in a highly diastereoselective manner. The scope of the reaction was investigated by varying substituents on the imine partner. This led to the synthesis of a broad range of analogues incorporating alkyl, aryl and heteroaryl functional groups, each isolated as a single diastereoisomer in 48-84% yield. Studies to develop an asymmetric variant of the reaction were performed, with Feringa's phosphoramidite ligand **299** enabling formation of the pyrrolidinone with a moderate 52% *e.e.* Analysis of the reaction mechanism and the origin of the observed diastereoselectivity have been investigated, followed by further functionalisation of the pyrrolidinone structure to yield a wide range of synthetically useful building blocks.

Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.* **2011**, *76*, 1961 (featured article).

Part 2: This section describes work towards the total synthesis of popolohuanone E (**1**), a marine natural product isolated from the *Dysidea sp.* sponge in 1990. The molecule contains a unique trihydroxylated dibenzofuran-1,4-dione core and two identical sesquiterpene units. The complex molecular structure and interesting biological activity of popolohuanone E (**1**) has made this compound a particularly interesting target.

Synthesis of model system **132** was successfully achieved, which allowed investigations into the key oxidative dimerisation reaction. Extensive studies led to isolation of the desired bis-quinone **133** in 40% yield, followed by acid catalysed cyclisation to form the dibenzofuran core present in popolohuanone E (**1**), in 26% yield. Focus then turned to the synthesis of the proposed precursor to popolohuanone E (**1**), 6'-hydroxyarenarol (**7**), based on the route developed within the Anderson group. Studies began with the enantioselective synthesis of intermediate iodide **83**

utilising Myers' *pseudo*-ephedrine auxillary. The remaining stereocentres were subsequently installed *via* an intramolecular Hosomi-Sakurai reaction in high yield and diastereoselectivity. With the *cis*-decalin framework in hand, construction of the phenolic portion was achieved by addition of lithiated 1,2,4-trimethoxybenzene to *neo*-pentyl aldehyde **74**, followed by deoxygenation using Barton-McCombie conditions. Installation of the *exo*-cyclic alkene, followed by removal of the three methyl ether protecting groups, then afforded the required precursor 6'-hydroxyarenarol (**7**). Finally, dimerisation was attempted as developed previously on model system **132**, however none of the desired bis-quinone (**18**) was observed.

Acknowledgements

I would firstly like to thank my supervisor Prof. Jim Anderson. He has allowed me to study two extremely interesting and challenging projects and has given me constant support and encouragement throughout my Ph.D. We have had many thought provoking discussions and I thank him for allowing me to develop my own research, with guidance and enthusiasm.

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In addition I am very greatful to the past and present members of the Anderson group, particularly those who enjoyed the move to London. These people have provided a fantastic working atmosphere, with many stimulating discussions, much enthusiasm and of course frequent social events.

Finally I would like to thank my family and friends, who have constantly supported me over the last three and a half years. I would particularly like to thank my Dad, Mum and my sister Claire for their encouragement and support. Special thanks go to Lynnie and Richard for putting a roof over my head and my partner Rich, who has done more than he knows. It is to these people that I dedicate this thesis.

Abbreviations

Å	angstrom(s)
AIBN	azobis(isobutyronitrile)
Anal.	analytical
app.	apparent
aq.	aqueous
Ar	aryl
Boc	*tert*-butyloxycarbonyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
BOX	bisoxazoline
br	broad
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
Calcd.	calculated
CAN	ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata
CI^+	positive ion chemical ionisation
COD	cyclooctadiene
COSY	correlation spectroscopy
Cq	quaternary carbon
CSA	camphorsulfonic acid
Cy	cyclohexyl
δ	chemical shift
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
DNA	deoxyribonucleic acid

d.r.	diastereomeric ratio
DTBP	4,4'-di-*tert*-butylbiphenyl
e.e.	enantiomeric excess
EI^+	positive ion electron impact
equiv.	equivalent(s)
e.r.	enantiomeric ratio
ES^+	positive ion electron spray
ESR	electron spin resonance
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
g	gram(s)
GABA	γ-aminobutyric acid
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
Imid	imidazole
IR	infra-red
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LB	Lewis base
LDA	lithiumdiisopropylamide
Lit.	literature
LUMO	lowest unoccupied molecular orbital
M	moles per litre
m	multiplet
M^+	molecular ion
m	*meta*

MBH	Mortia-Baylis-Hillman
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl ether
mp.	melting point
MS	molecular sieves
n	normal
NaHMDS	sodium bis(trimethylsilyl)amide
n-BuLi	normal-butyllithium
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholine *N*-oxide
nOe	nuclear Overhauser effect
o	*ortho*
OMB	*ortho*-methoxybenzyl
p	*para*
pet. ether	petroleum ether 40-60 °C
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
Py	pyridine
q	quartet
R	alkyl group
RAMP	(*R*)-(+)-1-amino-2-methoxymethylpyrrolidine
R_f	retardation factor

rt	room temperature
s	singlet
SAMP	(*S*)-(-)-1-amino-2-methoxymethylpyrrolidine
sat.	saturated
s-BuLi	secondary-butyllithium
SEM	(trimethylsilyl)ethoxymethyl
SET	single electron transfer
sept	septet
sext	sextet
sol.	solution
t	triplet
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
t-BuLi	tertiary-butyllithium
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMG	tetramethyl guanidine
TMS	tetramethylsilane
Tol	toluene
Ts	*p*-toluenesulfonyl
TTFA	thallium trifluoroacetate

Contents

Part 2: Towards the Synthesis of Popolohuanone E

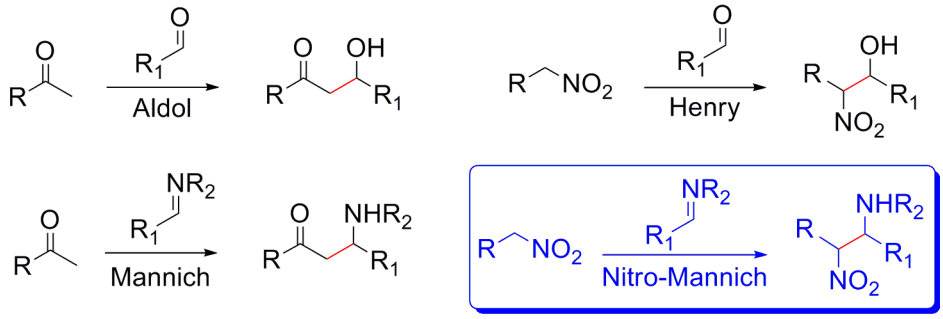
Part 1: Stereoselective Synthesis of Pyrrolidinones via Nitro-Mannich Reaction

1.0 Introduction

Development of concise processes in organic chemistry is a constant challenge. In addition, the synthesis of specific motifs, or functional groups is particularly important for the subsequent formation of more complex structures such as heterocyclic compounds and natural products. Processes that enable the synthesis of these motifs to be performed in an efficient and selective manner are therefore essential. This chapter aims to highlight the current literature reported within three areas, each of which is significant to the studies described in this thesis. The first section focuses on the nitro-Mannich (or aza-Henry) reaction, which has received considerable attention in recent years and has become an essential tool for the synthesis of β-nitroamines. Secondly, literature surrounding the conjugate addition to nitroalkenes is described, with particular focus on procedures that utilise this methodology in the nitro-Mannich reaction. This area has also been comprehensively studied due to the synthetic versatility of the nitro group and the ability to rapidly increase complexity within a molecule *via* this method. The final section focuses on the synthesis of pyrrolidinone heterocycles, which are noteworthy structures in the synthesis of pharmaceutical compounds and are the target structures in the research described herein.

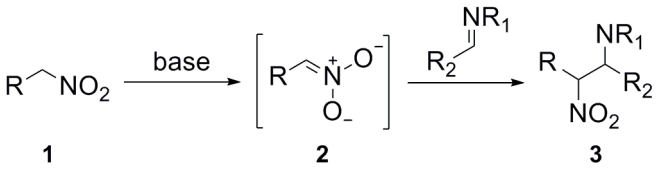
1.1 The Nitro-Mannich Reaction

The formation of a carbon-carbon bond is one of the most significant and synthetically useful processes within organic chemistry. Consequently, this process has been widely studied, with a number of significant reactions involving the addition of an active C-H nucleophile to a C=X electrophile. The most documented of these is the well-known aldol reaction,[1] which utilises the addition of an enolate to a carbonyl compound (Scheme 1.0). Analogous reactions such as the Henry reaction,[2] and the Mannich reaction,[3] are also well documented in the literature. Finally, the addition of a nitronate species to an imine is known as the nitro-Mannich or aza-Henry reaction, which had received little literature attention until 1998 when the first diastereoselective example was reported.[4] The following section will outline the development of the nitro-Mannich reaction, with particular focus on cascade or one-pot examples.



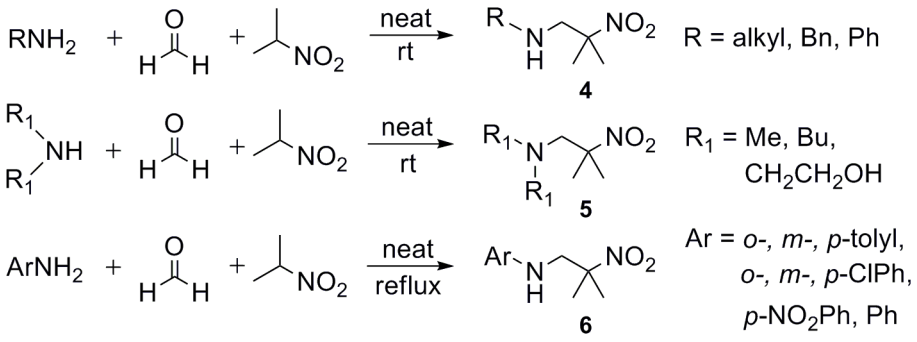
Scheme 1.0: Analogous carbon-carbon bond forming reactions.

First reported in 1896 by Henry,[5] the nitro-Mannich reaction predominantly involves formation of a nitronate species **2** followed by reaction with a suitable imine to afford the nitro-Mannich- or β-nitroamine product **3** (Scheme 1.1).



Scheme 1.1: Nitro-Mannich or aza-Henry reaction.

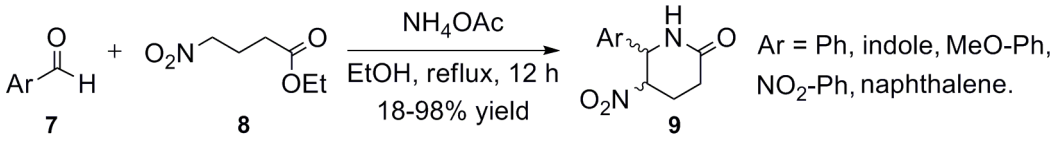
Subsequent to this, a number of reports were published in the early 1940's, involving the use of primary,[6] secondary,[7] and aromatic amines,[8] which upon reaction with formaldehyde and nitroparaffins, furnished the nitro-Mannich adducts **4-6** (Scheme 1.2).[9]



Scheme 1.2: Early nitro-Mannich examples.

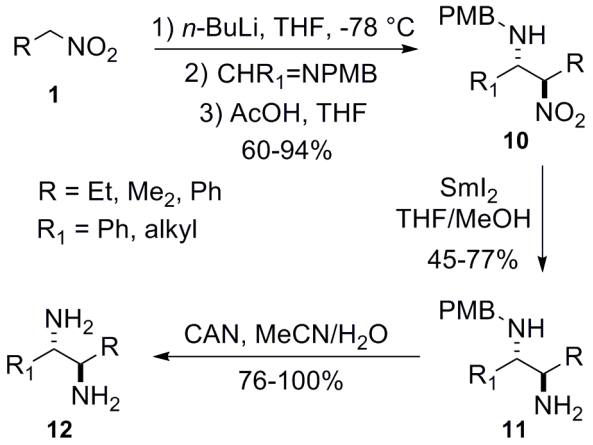
Following these studies, Jain *et al*. developed a direct nitro-Mannich reaction using ammonium acetate for the synthesis of piperidone analogues **9**.[10] Aromatic substituted aldehydes **7** were reacted with ammonium acetate and nitroester **8**, followed by lactamisation of the resulting nitroamine to yield the corresponding six membered piperidones **9** in variable yield (18-98%) (Scheme 1.3). Unfortunately,

when amines other than ammonia were used, the yields reduced considerably. Despite these significant early examples, it wasn't until 1998 when Anderson *et al.* reported the first diastereoselective nitro-Mannich reaction, that this area began to develop rapidly.[4]



Scheme 1.3: Nitro-Mannich reaction to form piperidones **9**.

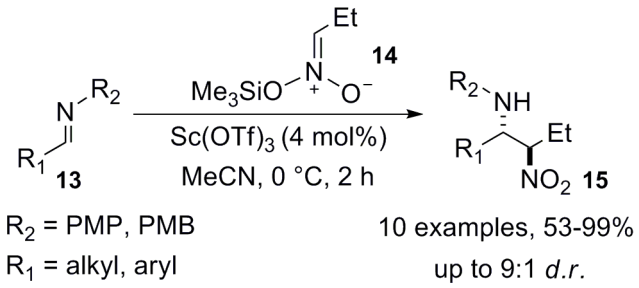
Anderson *et al.* reported the stereoselective addition of alkyl nitronate anions to a variety of substituted imines, bearing phenyl or alkyl substituents. Deprotonation of nitropropane using *n*-butyllithium generated the nitronate anion *in situ*, which underwent addition to various *N*-PMB protected imines in the presence of a Brønsted acid. This process enabled isolation of the *β*-nitroamines (**10**) in excellent yield (60-94%) with up to 10:1 diastereoselectivity in favour of the *anti* diastereoisomer. A six membered Zimmerman-Traxler like transition state, similar to that found in the aldol reaction,[11] was proposed to account for the observed selectivity. The nitro-Mannich products were subsequently reduced using samarium diiodide to give protected diamines **11** in good yield (45-77%), followed by removal of the PMB group using CAN, to afford the desired vicinal diamines **12** (Scheme 1.4).



Scheme 1.4: First diastereoselective nitro-Mannich reaction.

Following this work, the nitro-Mannich reaction was explored using silyl nitronates, promoted by Lewis acids such as $BF_3.Et_2O$, $TiCl_2(O\textit{i}\text{-}Pr)_2$ and lanthanide triflates.[12] This research was conducted with the intension of developing an enantioselective nitro-Mannich reaction using a chiral Lewis acid catalyst. The most promising results

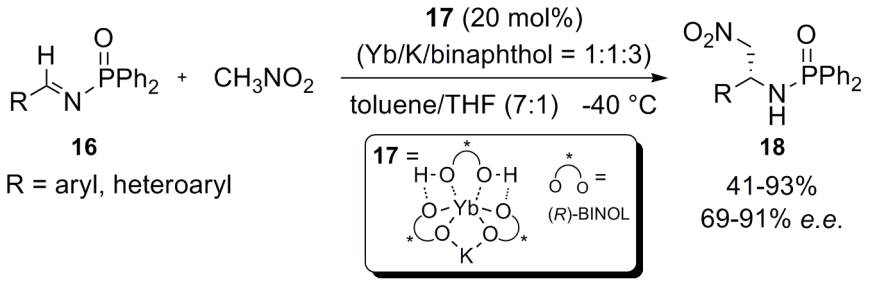
were obtained when using $Sc(OTf)_3$, which successfully promoted addition of trimethylsilyl nitronate **14** to *N*-protected imines **13**. Reactions were carried out to afford a range of β-nitroamines **15** in good yield (53-99%) and *anti* selectivity, (up to 9:1 *d.r.*) with a catalyst loading of just 4 mol%. Dramatic improvements both in yield and diastereoselectivity were found when using PMP protected imines rather than the previously used PMB protection (Scheme 1.5).



Scheme 1.5: Lewis acid catalysed nitro-Mannich reaction.

1.2 Metal Catalysed Nitro-Mannich Reactions

The first example of an enantioselective nitro-Mannich reaction was reported by Shibasaki in 1999.[13] Reactions between highly coordinating *N*-phosphinoyl imines **16** and nitromethane were performed in the presence of a ytterbium heterobimetallic catalyst system **17** to afford nitroamines **18** in good yield (41-94%) and *e.e.* (69-91%) (Scheme 1.6).



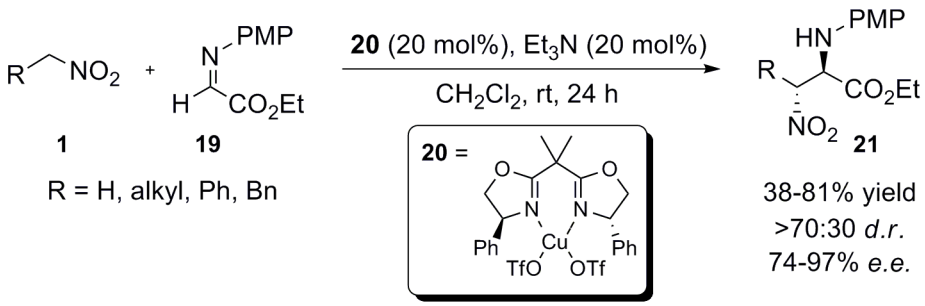
Scheme 1.6: First enantioselective nitro-Mannich reaction.

The reactive complex, comprising of $Yb(O\textit{i}\text{-}Pr)_3$, *t*-BuOK and (*R*)-binaphthol contained both Brønsted basic and Lewis acid functionalities, capable of activating both the electrophile and the nucleophile. The reaction proceeded smoothly using imines bearing aromatic electron-withdrawing substituents, however the corresponding electron-donating groups were found to require longer reaction times. Whilst this process was able to achieve high enantioselectivities, this system was

unable to promote the reaction with bulky substituents on the nitroalkane. The process also required particularly low temperatures and extremely slow addition of the nitro-partner (27 h) was required.

The same group later developed a similar BINOL-aluminium-lithium catalyst also using potassium *tert*-butoxide.[14] The results demonstrated that control of diastereoselectivity depended on solvent choice, with CH_2Cl_2 affording up to 7:1 diastereoselectivity in favour of the *anti* diastereoisomer. The β-nitroamine products were isolated in good yields (77-98%) and *e.e.* (60-83%) and the reaction was able to tolerate a variety of nitroalkanes, unable to react under the original conditions.

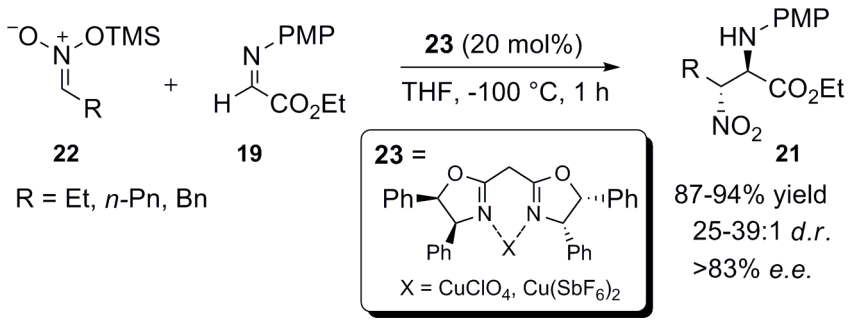
Subsequent to this work, Jørgensen and co-workers reported the stereoselective reaction between nitroalkanes **1** and *N*-PMP imine **19** derived from ethylglyoxylate. The process was conducted in the presence of a BOX-Cu(II) catalyst **20** to afford the desired β-nitro-α-amino esters **21**.[15] Reactions were conducted at ambient temperature and did not require an inert atmosphere or purification and drying of solvents. The β-nitroamines **21** were isolated in good yield (38-81%), with excellent *d.r.* and *e.e.* (Scheme 1.7).



Scheme 1.7: Enantioselective nitro-Mannich reaction using BOX-Cu(II) ligand (**20**).

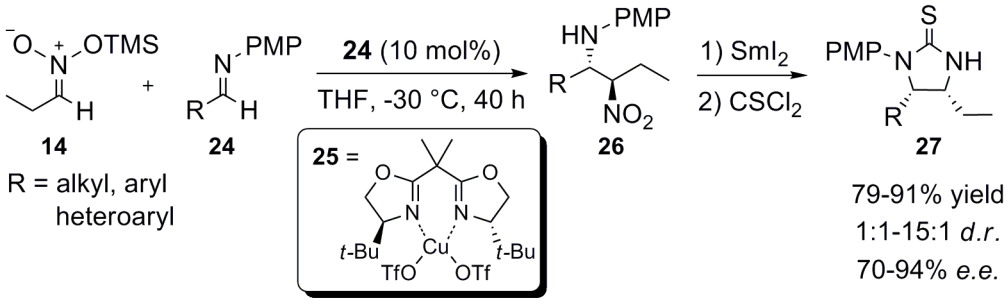
In addition to this work, the same authors published a highly diastereo- and enantioselective protocol, using silyl-nitronates **22** in the presence of Lewis acid catalyst **23**. When tosyl protected imino esters were utilised, the products were found to be unstable due to retro nitro-Mannich reaction or elimination of the nitro group. However when the more electron rich phenyl or PMP group was used, the products were obtained as stable nitroamines in good yield (87-94%). Reaction of imines **19** with a variety of alkyl silyl-nitronates **22** were carried out at –100 °C enabling the

amino-acid derivatives **21** to be isolated with high *d.r.* (25-39:1) and *e.e.* (<83%) (Scheme 1.8).



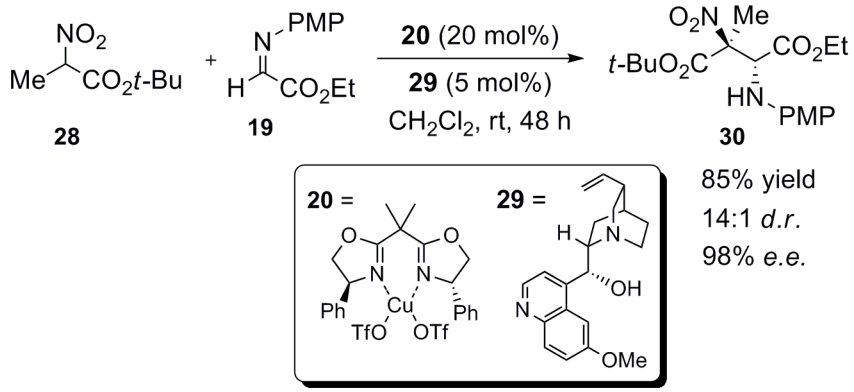
Scheme 1.8: First asymmetric nitro-Mannich using silyl-nitronates.

In 2005, the Anderson group reported a general asymmetric nitro-Mannich reaction, which proceeded with very low loading of both metal catalyst and chiral ligand.[16] The protocol was applicable to alkyl, aryl and heterocyclic substituted imines **24**, using a *t*-Bu-BOX-Cu(II) catalyst **25** and trimethylsilylnitropropanoate **14**. This led to high yields (79-91%) and selectivities (70-94% *e.e.*) for a broad range of β-nitroamine products **26** (Scheme 1.9). Previous studies had shown that the nature of the imine *N*-substituent had a significant effect on stereoselectivity, with OMB achieving higher diastereoselectivities due to a combination of chelation and steric factors.[17] However, under these conditions, it was found that when using OMB imines, the nitro-Mannich products were racemic. It was postulated that this was due to a facile, uncatalysed background reaction. In addition, chelation to the copper catalyst by the OMB group in a bidentate fashion could render the coordination sphere incapable of accepting the chiral ligand, therefore compromising its stereoinducing effect. The reaction scope was therefore demonstrated using *N*-PMP imines **24**. Absolute stereochemistry was determined by conversion to the corresponding thioimidazolidinone **27** by reduction with SmI_2 followed by reaction with thiophosgene. The use of sulfur as a heavy atom, allowed for accurate determination of the stereochemistry by X-ray crystallography (Scheme 1.9).



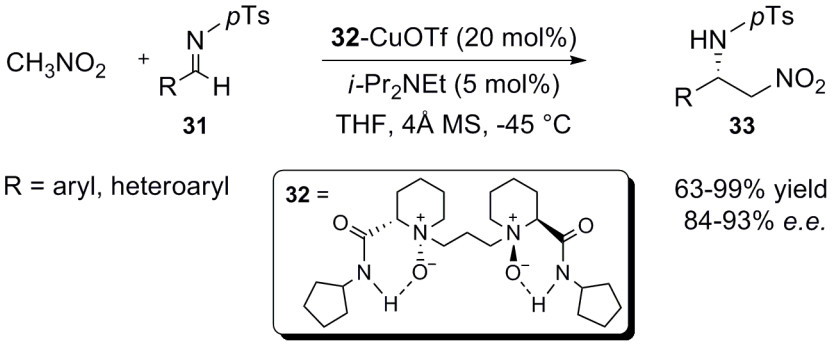
Scheme 1.9: Anderson's enantioselective nitro-Mannich protocol.

At a similar time, Jørgensen developed a dual activation protocol for the enantioselective nitro-Mannich reaction. This approach enabled formation of optically active quaternary centres by combination of previously used Lewis acid **20**, with the cinchona alkaloid **29**.[18] Reaction between nitro-ester **28** and PMP-imines derived from ethylglyoxylate (**19**) with only 5 mol% of the active catalyst led to an excellent yield (85%) and enantioselectivity (up to 98%) of the aminoacid derivatives **30** (Scheme 1.10).



Scheme 1.10: Dual activation in the enantioselective nitro-Mannich reaction.

In 2007, Feng and co-workers also found that the complex formed between Cu(I) triflate and *N,N*-dioxide **32** functioned as an efficient catalyst for the synthesis of β-nitroamines **33**.[19] Addition of nitromethane to *N*-tosyl protected imines **31** using a catalytic amount of Hünig's base, afforded the corresponding β-nitroamines **33** in good yield (63-99%) with excellent enantioselectivities (84-93%). The reaction was able to tolerate imines bearing both electron-withdrawing, electron-donating and heteroaryl imine substituents (Scheme 1.11).



Scheme 1.11: CuOTf /*N*,*N*,-dioxide catalysed nitro-Mannich reaction.

The authors proposed that both *N*-tosyl protected imine **31** and the corresponding nitronate, would form binding interactions with the catalyst to generate complex **34**. It was suggested that the chiral catalyst would position the nitronate on the *Re* face of the imine, which would be consistent with steric and electronic considerations. Nitro-Mannich reaction, followed by protonation allowed isolation of the β-nitroamines **33** and enabled efficient regeneration of the catalyst (Figure 1.0).

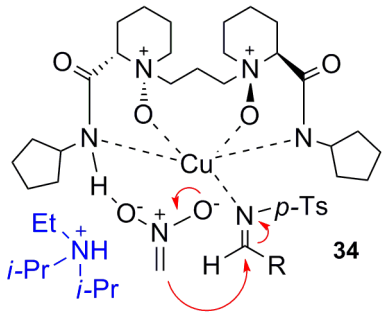
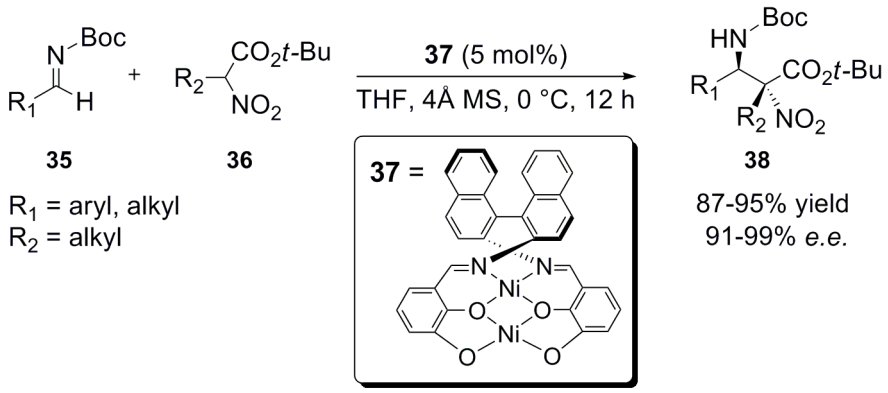


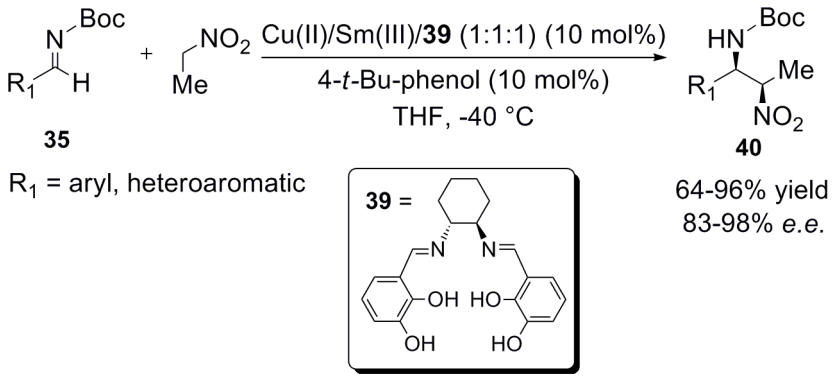
Figure 1.0: Proposed complex for the enantioselective nitro-Mannich reaction.

In addition to development of the first enantioselective nitro-Mannich reaction in 1999 (Scheme 1.6), Shibasaki *et al.* have made significant advances within the nitro-Mannich literature. This has included use of dinuclear nickel Schiff base complexes in the preparation of α-nitro-β-amino esters **38**.[20] Optimsation of the reaction conditions provided the best results when using nickel complex **37**. Reactions between *N*-Boc imines **35** bearing aromatic and alkyl substituents and *tert*-butyl nitroacetates **36** were performed in good yield (72-96%), *d.r.* (>87:13, *anti*:*syn*) and *e.e.* (>91%) (Scheme 1.12). The utility of the Ni_2 complex was further demonstrated in an analogous Mannich reaction between malonates and β-keto esters, again achieving high *e.e.* (91-99%).



Scheme 1.12: Ni_2 complex catalysed nitro-Mannich reaction.

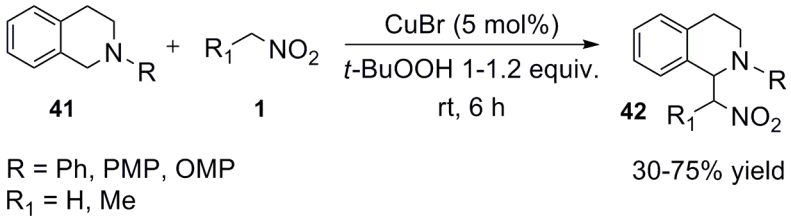
Shibasaki's work has also led to the first *syn* selective nitro-Mannich process.[21] This procedure utilised a heterobimetallic Cu-Sm-Schiff base complex **39** with *N*-Boc imines **35**, which proceeded to afford β-nitroamines **40** in good chemical yield (64-96%) with selectivities greater than 20:1 *d.r.* and up to 98% *e.e.* A variety of *N*-Boc imines **35** were used in the reaction bearing both aromatic and heteroaromatic substituents. The authors reported that both $Cu(OAc)_2$ and $Sm(O\textit{i}\text{-}Pr)_3$ were essential for achieving good reactivity and selectivity. In addition, it was reported that the 1:1 ratio of Cu and Sm and the addition of 4-*t*-Bu-phenol both resulted in beneficial effects on enantioselectivity (Scheme 1.13).



Scheme 1.13: The first *syn* selective nitro-Mannich reaction.

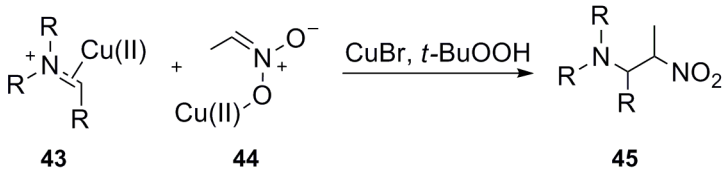
In contrast to the more traditional methods demonstrated within the nitro-Mannich literature, Li and co-workers developed a copper catalysed cross dehydrogenative coupling strategy, for a variety of sp^3 C-H bonds.[22] Coupling reactions between tetrahydroquinoline derivatives **41** and simple nitroalkenes **1** in the presence of CuBr (5 mol%) and *t*-BuOOH enabled oxidation to the corresponding iminium, followed by *in situ* nitro-Mannich reaction, to afforded the β-nitroamine products **42** in good

yield (30-75%) (Scheme 1.14). The reaction was also successfully applied to dimethylaniline derivatives and cyclic amines such as *N*-phenyl-pyrrolidines.



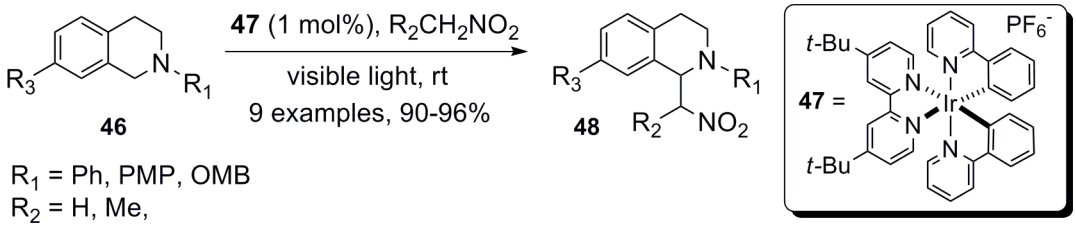
Scheme 1.14: Cross-dehydrogenative coupling nitro-Mannich reaction.

The authors proposed a possible pathway for the reactions. Copper catalysed H-abstraction of an sp^3 C-H adjacent to nitrogen could form the imine intermediate **43**, constructed by either a SET or ionic mechanism. The copper catalyst was also thought to activate the nitroalkane forming intermediate **44**. Subsequent coupling of the two intermediates would then result in the desired β-nitroamine products **45** with regeneration of the catalyst (Scheme 1.15).



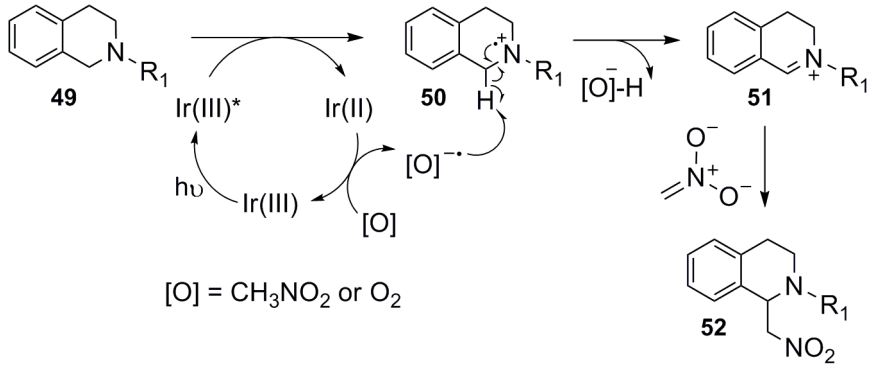
Scheme 1.15: Proposed pathway to cross coupling.

Finally, the scope of the metal catalysed nitro-Mannich reaction, is now expanding into more contemporary techniques within organic chemistry. Studies by Stephenson *et al.* utilised visible light photo-redox catalysis to carry out nitro-Mannich reactions *via* C-H functionalisation.[23] It was demonstrated that a variety of tetrahydroquinolines **46** could undergo C-H functionalisation using Ir(III) catalyst **47** which uniformly afforded the desired products **48** in excellent yields (>90%). Both nitromethane and nitroethane were used successfully and the reaction was generally insensitive to electronic effects with respect to substituents on the aromatic ring (Scheme 1.16).



Scheme 1.16: Iridium catalysed nitro-Mannich reaction.

The authors suggested that radical cation **50** could be formed by reductive quenching of the excited state iridium (III) complex by amine **49**, forming the powerful reducing agent Ir^{2+}. Catalyst turnover could subsequently be accomplished by reduction of nitromethane or oxygen to its radical anion, which could abstract a hydrogen atom from the trialkylammonium radical cation **50** forming iminium ion **51**. Addition of a suitable nitronate would then allow formation of the desired nitroamine products **52** (Scheme 1.17).

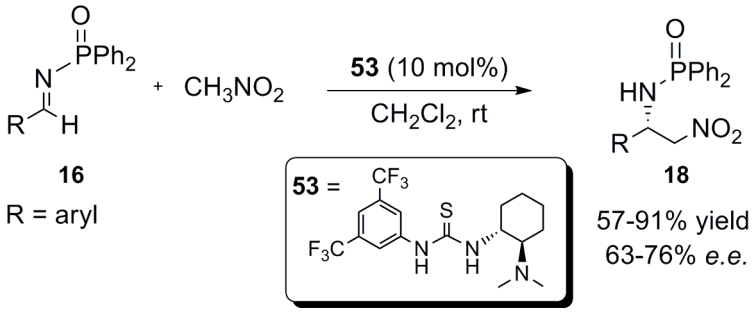


Scheme 1.17: Nitro-Mannich reaction *via* C-H functionalisation.

1.3 The Organocatalytic Nitro-Mannich Reaction

Organocatalysis is a rapidly expanding area in asymmetric organic synthesis.[24] Catalysts of organic origin are advantageous compared to their metallic counterparts due to their increased stability, as well as being inexpensive and less toxic. Catalysts of this type have been shown to achieve outstanding enantio- and diastereoselectivities,[25] which has resulted in the organocatalysed nitro-Mannich reaction receiving considerable attention.

The first organocatalysed nitro-Mannich reaction was reported by Takemoto and co-workers in 2004.[26] This methodology was developed using bifunctional thiourea catalyst **53** with *N*-phosphinoyl protected imines **16**. Reactions were performed using a variety of aromatic imines, with thiourea catalyst **53** (10 mol%) and ten equivalents of nitromethane or nitroethane, to yield the corresponding β-nitroamines **18** in good yield (57-91%) and moderate *e.e.* (63-76%). It was noted that the use of electron-donating or electron-withdrawing groups did not affect selectivity and when using a sterically hindered imine substituent (2-naphthyl), the enantioselectivity was slightly increased (Scheme 1.18).



Scheme 1.18: First organocatalytic nitro-Mannich reaction.

The proposed mechanism of activation was based on previous studies involving the Michael addition of malonates to nitroolefins.[27] The authors postulated that hydrogen-bonding interactions between the thiourea moiety of the catalyst and the nitro group would allow formation of species **55**. Subsequent deprotonation by the neighbouring tertiary amino group would then generate the desired nitronate species **56** (Figure 1.1).

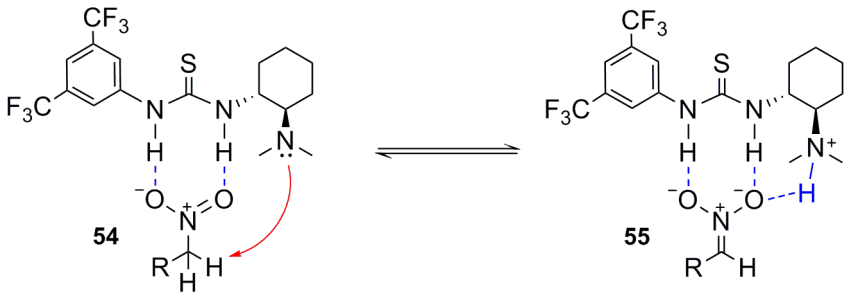
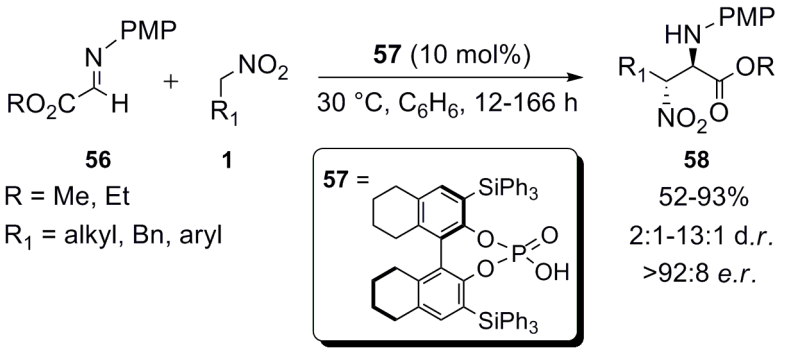


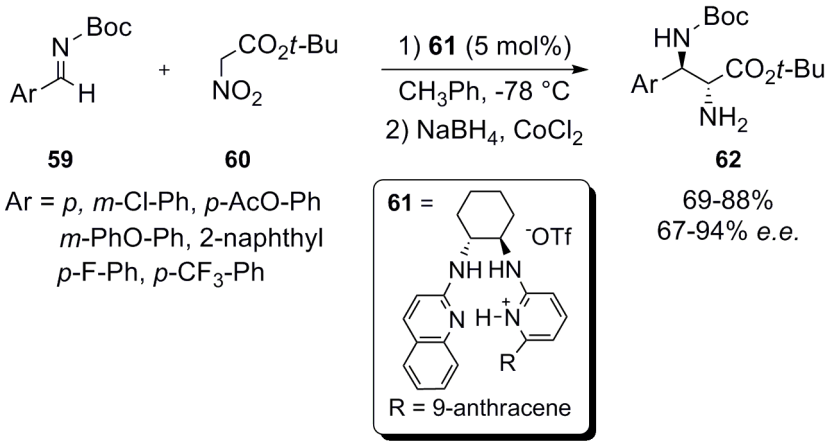
Figure 1.1: Proposed activation by thiourea catalyst **53**.

In contrast to the work described above, a number of reports within the nitro-Mannich literature have made use of a chiral Brønsted acid catalyst. In 2008, Rueping *et al*. reported a direct nitro-Mannich reaction using a variety of nitroalkanes **1** with *N*-PMP protected imines **56** derived from methyl or ethyl glyoxylate.[28] The reaction employed a chiral BINOL phosphonate catalyst **57** to afford the desired β-nitroamines **58** in good yield (53-93%), with up to 13:1 selectivity in favour of the *anti* isomer and excellent *e.r.* (>92:8). The authors also proposed a bifunctional role for the catalyst involving coordination to the imine as well as promoting the shift in equilibrium position between the nitroalkane and corresponding nitronate (Scheme 1.19).



Scheme 1.19: Bifunctional BINOL catalysed nitro-Mannich reaction.

Complimentary to this work, Johnston *et al*. published a 'chiral proton catalysed' enantioselective addition of nitroacetic acid derivatives **60** to a variety of *N*-Boc protected aromatic imines **59**.[29] The authors identified complex **61** as a suitable catalyst for the reaction, which was applicable to a wide variety of aromatic substituents on the imine. Subsequent reduction using a sodium borohydride/cobalt (II) chloride system afforded high overall yields (69-88%) and *e.e.* (67-94%) of the desired diamines **62** (Scheme 1.20).



Scheme 1.20: Johnston's bifunctional catalyst system.

More recently, Johnston has developed this procedure further, with slight modifications to the catalyst.[30] Incorporation of a methoxy substituent (**63**), allowed for improved enatioselectivities, which were attributed to the increased rate of the reaction. In this case the products were isolated as the *syn* diastereoisomer in >20:1 *d.r.* and up to 99% *e.e.*, however a proposal for the origin of this selectivity was not reported. The catalyst was subsequently modified further, to furnish catalyst **64** incorporating two pyrrolidine groups.[31] This allowed the coupling of nitroethane and

N-Boc protected imines **59** to be performed, affording the *anti* diastereoisomer of the β-nitroamines in excellent yield (61-100%) and *e.e.* (87-95%) (Figure 1.2).

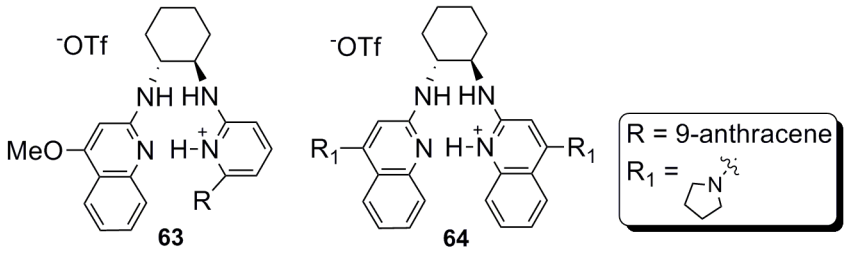
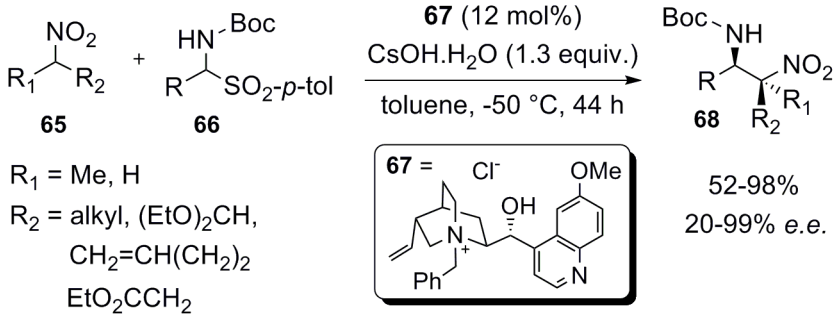


Figure 1.2: Further modification to Johnston's catalyst.

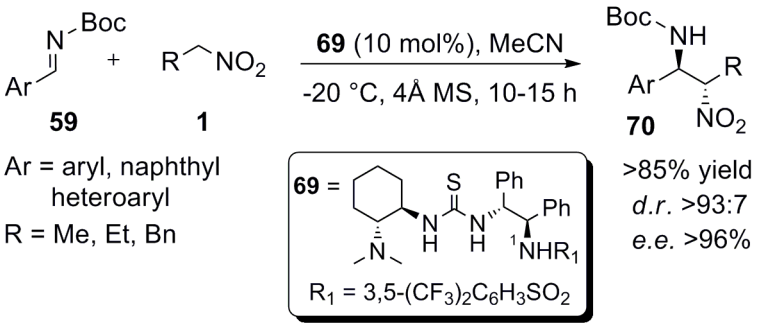
Complimentary to the organocatalysed reactions described above, Palomo *et al.* reported an efficient asymmetric nitro-Mannich reaction, performed under phase transfer conditions, in the presence of cinchone-derived ammonium catalyst **67**.[32] Reaction of nitroalkanes **65** with amido sulfones **66** using $CsOH{\cdot}H_2O$ proceeded smoothly to furnish nitroamines **68** in good yield (52-98%), modest *d.r.* (2-9:1) and variable *e.e.* (20-99%). The reaction tolerated a wide range of amido sulfones **66** including enolisable substrates. In addition, this report improved on previous work within the same group,[33] utilising a range of functionalised nitroalkanes **65** (Scheme 1.21).



Scheme 1.21: Phase transfer catalysed nitro-Mannich reaction.

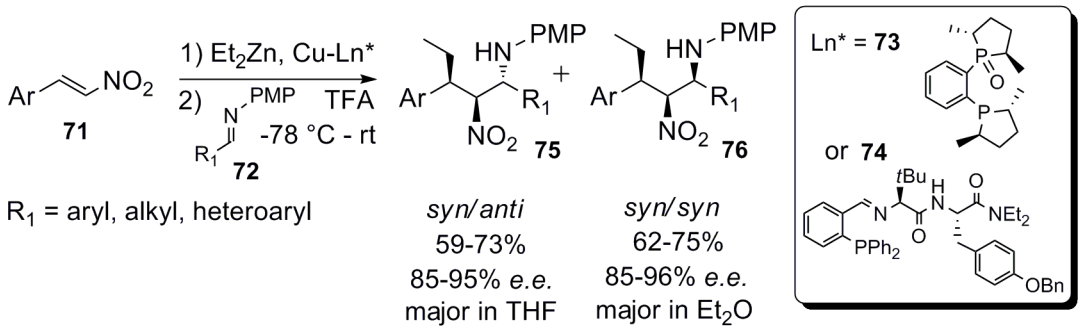
The use of thiourea organocatalysis has now been applied extensively to the nitro-Mannich reaction,[34] with one of the most efficient procedures reported by Wang *et al.* in 2008.[35] Nitro-Mannich reaction between simple nitroalkanes **1** and *N*-Boc imines **59** were carried out in the presence of bifunctional amino-thiourea catalyst **69** bearing multiple hydrogen bond donors. It was found that when using a similar catalyst with a methylated nitrogen at position 1, the reaction became slower and only a 20% yield was obtained. This indicated that a third donor at this position had a significant role in the enantioselective reaction, although mechanistic details were not reported.

Reactions were performed using imines bearing electron donating and electron withdrawing groups, leading to the corresponding β-nitroamine products **70** in outstanding yield (85-99%) and *e.e.* (96-99%). The authors also noted that the position and electronic properties of substituents on the aromatic ring had limited effect on enantioselectivity (Scheme 1.22).



Scheme 1.22: Highly selective thiourea catalysed nitro-Mannich reaction.

Finally, during this research program, Anderson and co-workers published the enantioselective conjugate addition/nitro-Mannich reaction forming two carbon-carbon bonds and three contiguous stereocentres in a one-pot process.[36] Conjugate addition of diethylzinc to a variety of aromatic nitroalkenes was controlled by known chiral copper-ligand catalysts (**73** and **74**). Reaction of the resulting nitronate anion with aromatic and alkyl substituted *N*-PMP protected imines **72** gave the β-nitroamine products **75** or **76** in good yield (59-75%), with high enantioselectivities (85-96%). Choice of solvent dictated the selectivity of the reaction with THF affording a homogenous reaction mixture, providing the *syn/anti* diastereoisomer and Et_2O or toluene affording a heterogeneous reaction mixture, to yield the corresponding *syn/syn* isomer. These observations were explained by the presence of a closed and open transition state respectively. This report represents an efficient method for the selective formation of either β-nitroamine diastereoisomer and is a rare example of a *syn* selective nitro-Mannnich reaction (Scheme 1.23).

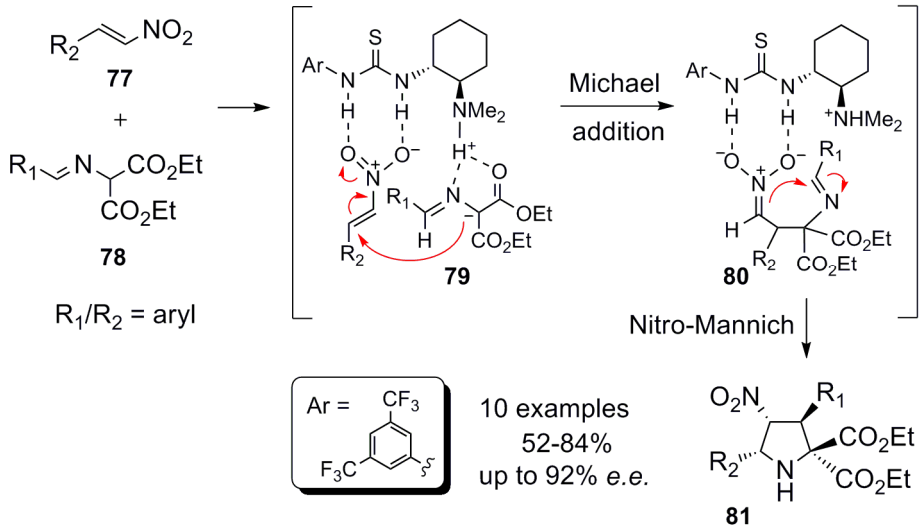


Scheme 1.23: Stereoselective conjugate addition/nitro-Mannich protocol.

1.4 Cascades Involving the Nitro-Mannich Reaction

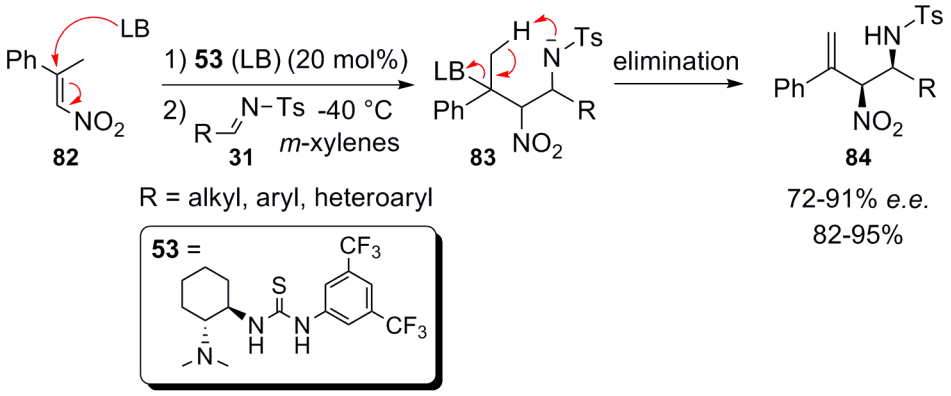
A cascade or tandem process in organic chemistry refers to a consecutive series of reactions, which provides an efficient method for the formation of complex multifunctional molecules in one step, or what has become known as a 'one pot' reaction. In recent times, literature describing these processes has expanded greatly, enabling us to create expedient routes to complex, highly functionalised molecules. These processes also provide environmental and economical advantages in a wide variety of disciplines within organic chemistry.[37] To date there are a limited number of examples of cascade reactions utilising the nitro-Mannich reaction, the most important of which are reported here.

In 2008 Takemoto and co-workers,[38] utilised the nitro-Mannich in a formal [3+2] cycloaddition reaction, catalysed by a thiourea catalyst. It was suggested that nitroalkenes **77** and α-amino malonate imine **78** would be anchored and activated through hydrogen bonding systems between the amine and thiourea moieties of the catalyst (species **79**) and as a result, the enantioselective Michael addition would proceed *via* a zwitterionic intermediate **80**. An intramolecular nitro-Mannich reaction could then afford the highly functionalised pyrrolidine ring structure. Scope of the reaction was investigated with respect to substituents on both the imine **78** and the nitroalkene partners **77** to afford the pyrolidines **81** in good yield (52-84%) and high selectivity (up to 98:1:1 *d.r*. and 92% *e.e.*) (Scheme 1.24).



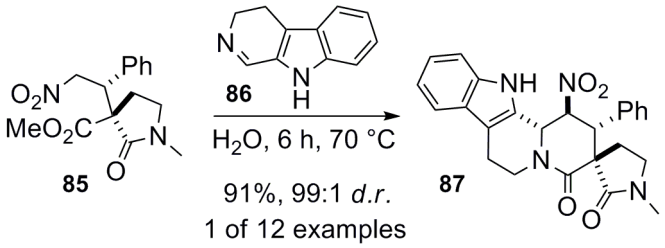
Scheme 1.24: Formal cycloaddition reaction involving the nitro-Mannich reaction.

In 2009, Xu and co-workers reported a tandem aza-Morita-Baylis-Hillman/nitro-Mannich reaction using substituted nitroalkene **82** and *N*-tosyl protected imines **31**.[39] Reversible conjugate addition of the nucleophilic catalyst **53** to nitroalkene **82** generated the corresponding nitronate, which was postulated to intercept imine **31** to afford intermediate **83**. The desired products were then generated by elimination and hence regeneration of the catalyst. The thiourea catalyst **53** was designed to allow initial attack on the nitroalkene by the tertiary amino group as well as allowing activation of the imine *via* hydrogen-bonding. The scope of the reaction was investigated using a variety of *N*-tosyl imines **31** in *m*-xylenes at -40 °C to afford the corresponding products **84** in excellent yield 80-95% and *e.e.* (87-91%) for substrates containing electron-rich groups. It was noted that when using electron-deficient substituents a slight decrease in enantioselectivity was seen (72-77% *e.e.*) (Scheme 1.25).



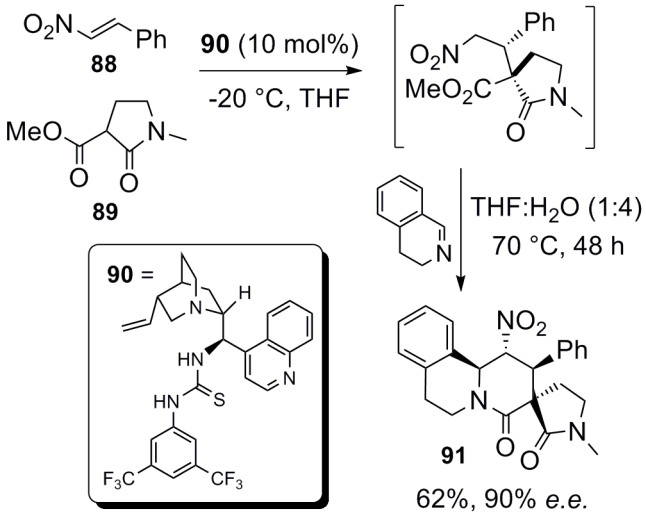
Scheme 1.25: Tandem Baylis-Hillman/nitro-Mannich reaction.

Dixon *et al.* reported a nitro-Mannich/lactamisation cascade of γ-nitro esters **85** with cyclic imines **86** in the preparation of multicyclic piperidinone ring structures.[40] The resulting piperidinone structures **87** are commonly found in many complex alkaloid natural products such as reserpine,[41] and nakadormarin A (see section 1.5).[42] In contrast to the majority of nitro-Mannich literature, this process demonstrates the use of highly functionalised nitroalkanes **85**, synthesised *via* conjugate addition of the corresponding pyrrolidinone to nitrostyrene. Nitro-Mannich reaction between the nitronate formed from nitroalkane **85** and cyclic imine **86**, followed by lactamisation of the resulting β-nitroamine, afforded the desired products **87**. The reaction was successful using a number of cyclic imines and nitroesters to furnish the pentacyclic products **87** in good yield (58-91%), with excellent *d.r.* (>94:6) (Scheme 1.26).



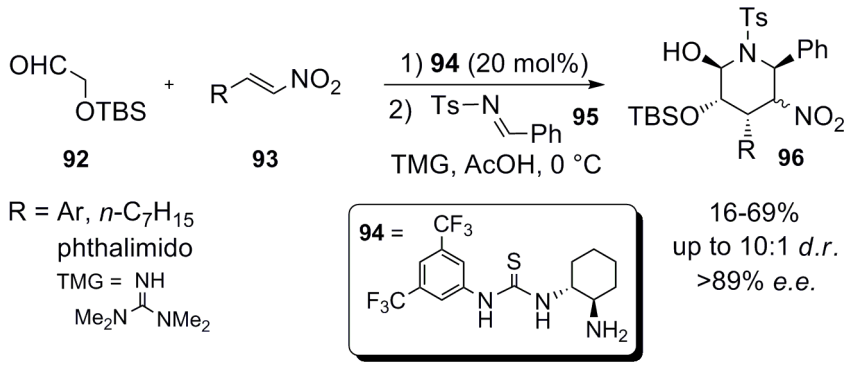
Scheme 1.26: Piperidinone formation *via* nitro-Mannich/lactamisation reaction.

This methodology was subsequently extended to a 'one pot' enantioselective, three component coupling reaction, employing cinchona catalyst **90**.[43] Use of THF in place of previously used H_2O was required for the 1,4-addition reaction, however it was found that subsequent addition of H_2O at the nitro-Mannich stage allowed the reaction to proceed as previously developed. The desired piperidinone **91** was successfully isolated in 62% as a single diastereoisomer in 90% *e.e.* (Scheme 1.27).



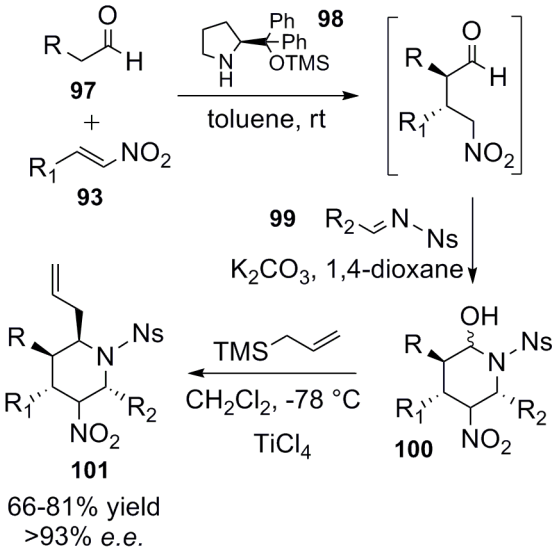
Scheme 1.27: Enantioselective conjugate addition/nitro-Mannich reaction.

Complimentary to this work, Barbas (III) published a one-pot synthesis of six membered imino sugar derivatives **96** using the nitro-Mannich reaction.[44] Organocatalysed asymmetric Michael addition of *tert*-butyldimethylsilyl-oxyacetaldehyde **92** to range of nitroolefins **93** were performed, employing the thiourea catalyst **94**. Nitro-Mannich reaction with tosyl protected imine **95** provided the imino sugars **96** containing five contiguous stereocentres in high *e.e.* (>89%). Unfortunately, the diastereoselectivity for this reaction ranged from 3:1-10:1 depending on substituents and provided only modest yields (16-69% as a mixture of diastereoisomers) (Scheme 1.28).



Scheme 1.28: One-pot procedure for the synthesis of imino sugars **96**.

Finally, Hayashi *et al.* have recently reported the enantioselective synthesis of piperidines by coupling of four components in a 'one pot' sequence.[45] Nitrostyrene **93** was treated with propanal **97** in the presence of proline derivative **98** (5 mol%), in toluene over 7 hours. Subsequent reaction with nosyl protected imines **99** in the presence of K_2CO_3, was carried out to undergo *in situ* nitro-Mannich and lactamisation reaction, affording intermediate **100**. The solvent was then exchanged from a toluene/1,4-dioxane system to CH_2Cl_2 to allow allylation to be performed in the presence of $TiCl_4$, to yield the corresponding piperidines **101** as a single diastereoisomer. Scope of the reaction was examined using a variety of aromatic substituted imines, as well as variation of the aldehyde and nitrostyrene, to give the desired piperidines **101** in good yield (66-81%) and *e.e.* (>93%) each as a single isomer (Scheme 1.29).



Scheme 1.29: One pot, four component nitro-Mannich reaction.

1.5 The nitro-Mannich Reaction in Synthesis

The nitro-Mannich reaction has now been significantly developed to afford the β-nitroamine products in an efficient and selective manner.[46] The reaction can be applied to a large array of substrates to afford selectively either the *anti* or *syn* diastereoisomer in high yield and *e.e.* The β-nitroamine products have therefore been utilised to synthesise complex structural motifs leading to biologically active natural products and pharmaceutical compounds.

Direct reduction of the β-nitroamine nitro-Mannich products is also a noteworthy transformation, leading to an efficient synthesis of 1,2- or vicinal diamines. This cyclic or acyclic motif is important throughout organic chemistry and is found in many biologically active natural products, chiral ligands and Schiff base complexes (Figure 1.3).[47]

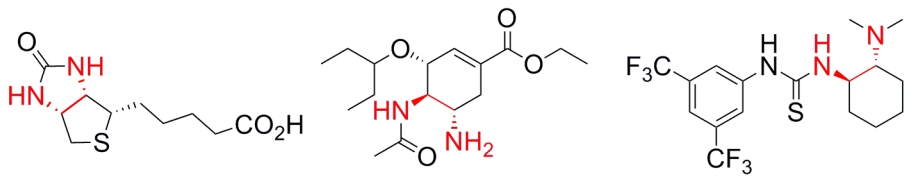
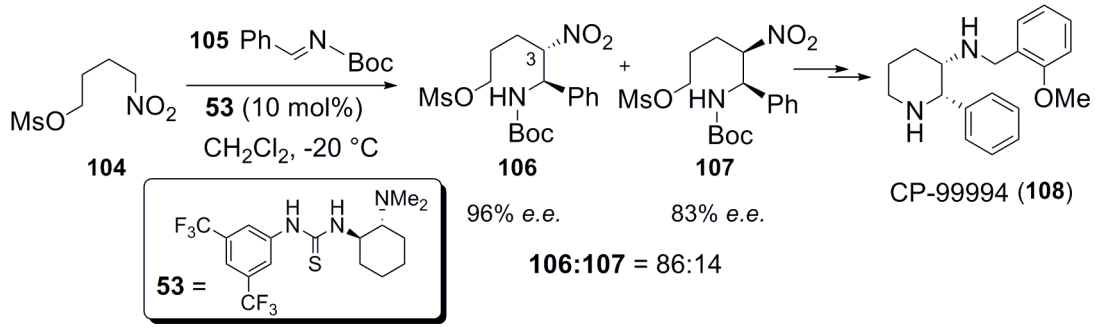


Figure 1.3: Vicinal diamines examples in natural products and ligands.

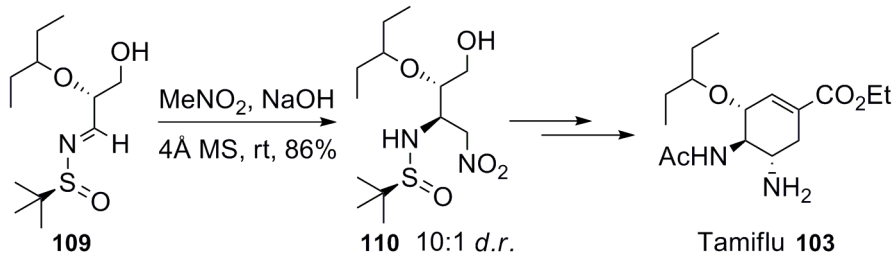
The nitro-Mannich reaction has now been utilised in a variety of syntheses, including two syntheses of the diamine CP-99994 (**108**) by Takemoto,[48] and Shibasaki.[49]

Takemoto's synthesis involved nitro-Mannich reaction between nitroalkane **104** and Boc-protected imine **105** in the presence of thiourea **53**, to furnish a 86:14 ratio of *trans*:*cis* isomers (**106** and **107**) in high *e.e.* (Scheme 1.30). Final steps involved cyclisation, followed by epimerisation of the stereocentre at the C3-position to afford the desired *cis*-isomer. Subsequent reduction of the nitro-group and reductive amination with 2-anisaldehyde in the presence of $NaBH_3CN$ and AcOH afforded the target CP-99994 (**108**) (Scheme 1.30).



Scheme 1.30: Takemoto's synthesis of CP-99994 (**108**).

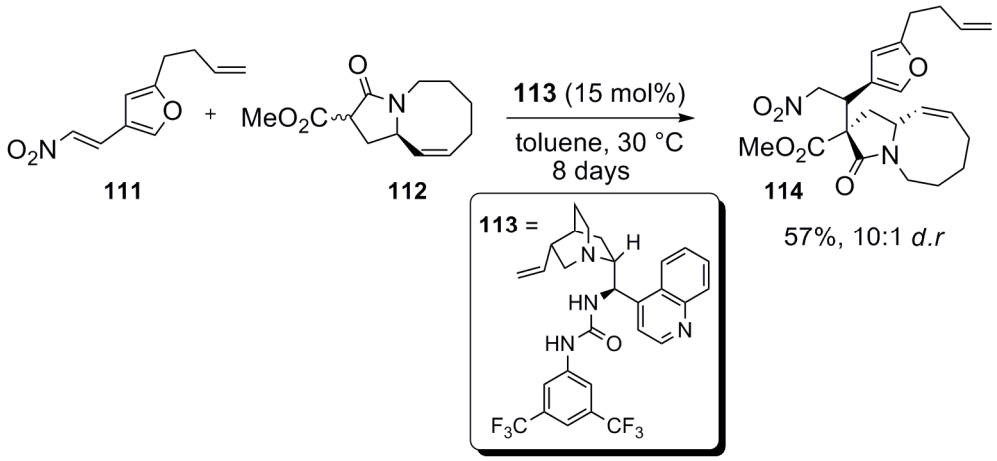
Lu *et al*. have also utilised the nitro-Mannich reaction in their practical, azide free approach to tamiflu (seltamivir) (**103**) from diethyltartrate.[50] Asymmetric nitro-Mannich reaction was performed using nitromethane and imine **109** bearing an enantiopure sulfoxide *N*-protecting auxillary. The reaction was carried out in the presence of NaOH (5 equivalents) to afford a 10:1 mixture of nitroamine **110** in 86% yield. The diastereoisomers were separated by column chromatography and the major isomer used in the final steps towards the target **103** (Scheme 1.31).



Scheme 1.31: Synthesis of tamiflu (**103**) using the nitro-Mannich reaction.

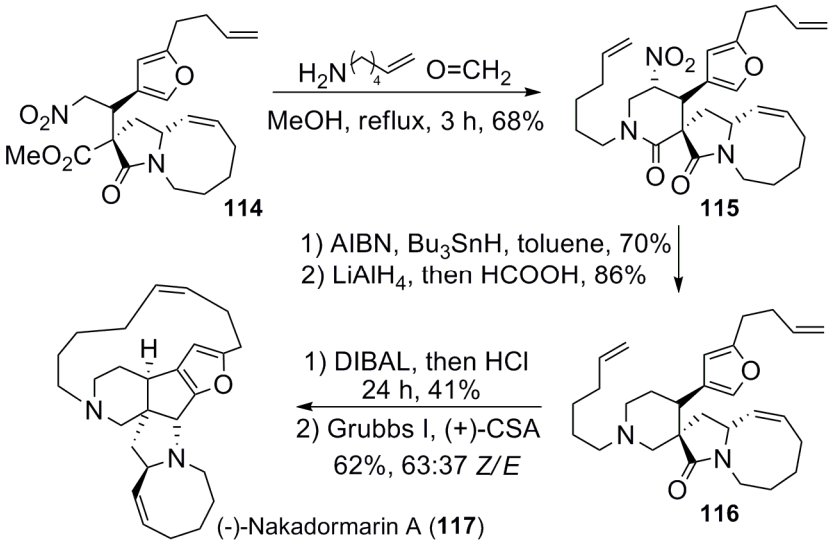
More recently Dixon *et al.* have reported an elegant synthesis of (-)-nakadormarin A (**117**), a marine alkaloid of the manzamine family, showing cytotoxic activity against murine lymphoma L1210 cells (IC_{50} = 1.3μg/mL).[51] This synthesis successfully utilised a nitro-Mannich/lactamisation reaction as the key step. Initial studies focussed on the conjugate addition of pyrrolidinone **112** to nitroalkene **111**. Use of

stoichiometric quantities of KHMDS and NaHMDS were found to afford a mixture of diastereomeric products, which prompted the authors to investigate alternative strategies. After extensive optimisation, the reaction was found to be successful using a bifunctional cinchona catalyst **113**,[52] which facilitated the diastereoselective Michael addition to afford **114** in good yield (57%) and as a 10:1 mixture of diastereoisomers (Scheme 1.32).



Scheme 1.32: Conjugate addition strategy towards (-)-nakadormarin A (**117**).

Subjection of **114** to the proposed nitro-Mannich/lactamisation cascade previously reported,[53] facilitated construction of the spirocycle **115** in an excellent 68% yield. Reduction of the nitro group was achieved using a modification of a procedure developed by Ono,[54] in 70% yield. With this in hand, low temperature $LiAlH_4$ reduction facilitated exclusive delivery to the carbonyl of the *δ*-lactam, which on direct reduction of the resulting hemiaminal, using formic acid, allowed formation of mono-lactam **116** in 86% yield. After significant optimisation, single hydride delivery to the remaining lactam was achieved using DIBAL, which was followed by highly stereoselective acid mediated cyclisation to furnish the corresponding pentacycle in 41% yield. The synthesis was concluded with a *Z*-selective olefin metathesis (63:37 *Z*/*E*), achieved using Grubb's first-generation catalyst in the presence of excess (+)- or (-)-CSA, to afford (-)-nakadormarin A (**117**) in 62% yield, completing the total synthesis (Scheme 1.33).



Scheme 1.33: Dixon's synthesis of (-)-nakadormarin A (**117**).

Research involving the nitro-Mannich reaction is now expanding into a variety of efficient tandem or cascade approaches. Complimentary to this, research within the Anderson group has focused on the development of a tandem 1,4-addition/nitro-Mannich reaction, which has been utilised in the research described herein. Relevant literature surrounding the conjugate addition to nitroalkenes and nitroacrylates is therefore reviewed in the following section.

1.6 Stereoselective Conjugate Addition to Nitroalkenes

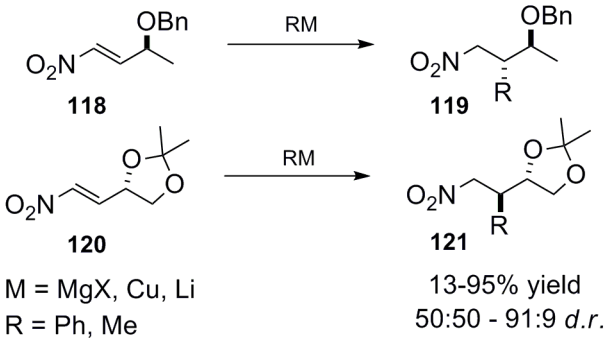
Nitroolefins stand out as particularly versatile molecules within organic chemistry.[55] The highly electron withdrawing nitro group, makes these olefins particularly susceptible to nucleophilic 1,4-conjugate addition. The range of nucleophiles employed in Michael additions to nitroalkenes is now extensive and includes carbon, oxygen, nitrogen, sulfur and phosphorus based examples.[56] This methodology can therefore enable the synthesis of more complex building blocks in a catalytic and selective manner. When considering the nitro-Mannich reaction, conjugate addition to a nitroolefin, can allow *in situ* generation of the desired nitronate. This process could enable the scope and functionality with respect to the nitronate partner to be greatly increased and is therefore an interesting objective for synthetic methodology.

In addition, the nitro group itself is particularly versatile in synthesis and can be transformed into a variety of functional groups. Conversion to the corresponding carbonyl, known as the Nef reaction,[57] as well as reduction to the corresponding

hydroxylamine or amine are important transformations, which can lead to the synthesis of highly functionalised molecules.[58] The research described in this thesis aims to utilise the nucleophilic addition of a diorganozinc reagent to a suitable nitroacrylate, therefore the majority of this report will focus on the addition of carbon nucleophiles to nitroalkenes and nitroacrylates.

1.6.1 Substrate/Auxillary Controlled Conjugate Addition

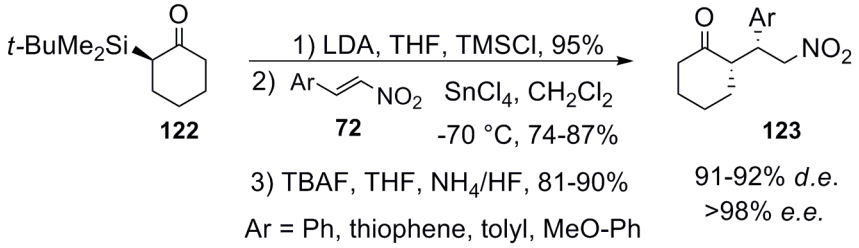
In 1996, Cossio *et al.* reported the stereoselective conjugate addition of carbon nucleophiles to chiral (*E*)-nitroalkenes.[59] Nitroalkenes **118** and **119** were treated with a variety of nucleophilic reagents to afford products **120** and **121** in variable yield (13-95%) and modest selectivity in favour of the *anti* diastereoisomer. It was noted that the stereoselectivity of methyl nucleophiles was comparatively low, (55:45-76:24 *anti:syn)* however no suggestions as to the reason for this low selectivity were reported. The authors found that stereocontrol was slightly improved by the use of excess lithium salts, with the best results achieved when using lithium diphenyl cuprate (Scheme 1.34).



Scheme 1.34: Stereoselective addition of carbon nucleophiles.

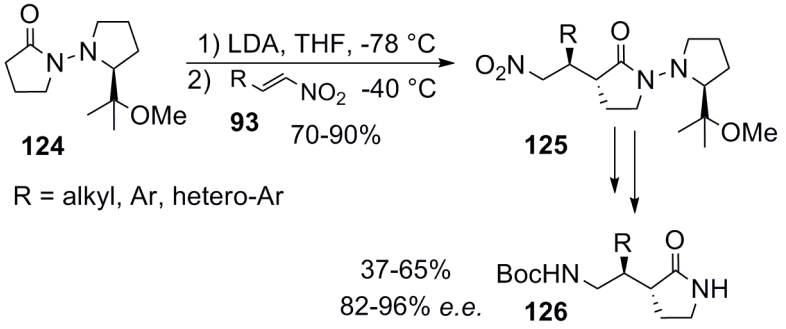
In 1999, Enders *et al.* reported the use of chiral α-TBDMS ketones **122** to control stereoselectivity in the synthesis of cyclic and acyclic α,β-disubstituted-nitro ketones **123**.[60] The α-TBDMS ketones **122** were prepared using SAMP/RAMP chiral auxillary methodology, previously developed.[61] Ketone **122** was converted into the kinetic trimethylsilyl enol ether, by treatment with lithium diisopropylamide and chlorotrimethylsilane in good yield (95%). Subsequent treatment with a variety of nitrostyrenes **72** in the presence of $SnCl_4$, provided the conjugate addition products in good yield (74-87%) with high asymmetric induction. Removal of the α-TBDMS

group was then achieved using TBAF to afford the desired γ-nitro ketones **123** in excellent yield (81-90%) and *e.e.* (>98%) (Scheme 1.35).



Scheme 1.35: Conjugate addition using silyl enol ether control.

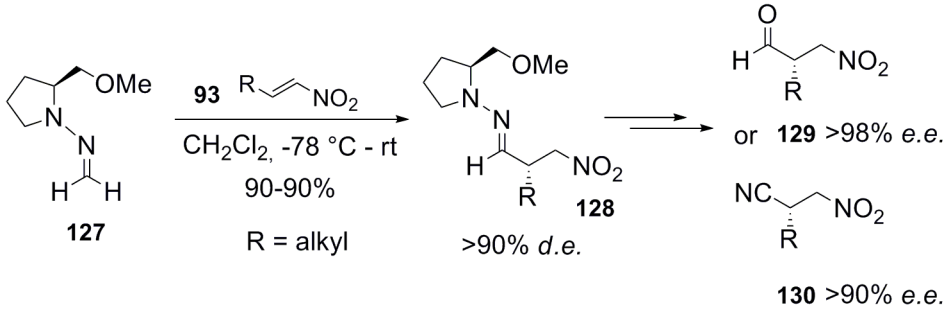
The conjugate addition of proline derived chiral auxillaries has been demonstrated as a useful method for the production of pharmacologically interesting precursors to GABA analogues.[62] Conjugate addition of γ-lactam **124** bearing a sterically demanding (*S*)-proline derived auxillary, was performed to afford the functionalised lactam derivatives **125**. It was reported that addition to aliphatic nitroalkenes, were found to produce higher *d.e*. (80-90%) when compared to the corresponding aromatic analogues (50-78%). Reduction of the nitro group, followed by Boc protection and removal of the chiral auxillary, afforded the desired lactams **126** in moderate yield (37-65%) and diastereoselectivity (82-96% *d.e.*) (Scheme 1.36).



Scheme 1.36: Formation of GABA analogues *via* conjugate addition.

Use of functional groups such as SAMP-hydrazones have also been reported to control stereoselective addition to nitroalkenes.[63] Addition of aza-enamine **127** derived from formaldehyde to nitroalkenes **93** were performed under neutral conditions to afford addition product **128**. Conversion to the corresponding aldehyde **129** or nitrile **130** occurred without epimerisation, to provide the desired compounds in good yield and enantioselectivity (Scheme 1.37). In addition, experiments were carried out using formaldehyde SAMP or RAMP-hydrazones with nitroalkenes

bearing chiral sugar derived substituents. This methodology also led to excellent yields (71-95%) and high diastereoselectivities (>96% *d.e.*) of the Michael addition products.



Scheme 1.37: Conjugate addition using SAMP/RAMP hydrazones.

Mechanistic analysis proposed a closed transition state in which the SAMP-hydrazone would attack the *Si* face of the nitroalkene in a chair like transition state (**131**). It was suggested that the transition state would also be stabilised by the attractive electrostatic interactions between the developing charges (N δ^+ and NO_2 δ^-) (Figure 1.4).

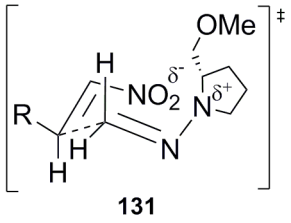


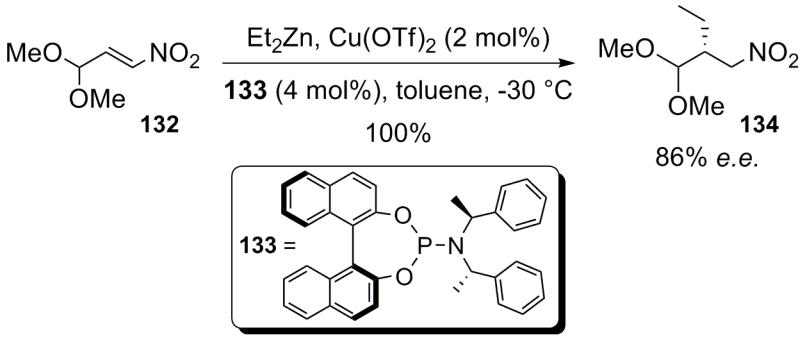
Figure 1.4: Proposed transition state for SAMP-hydrazone conjugate addition.

1.6.2 Catalytic Conjugate Addition

In addition to auxillary based conjugate additions, the ability to carry out a catalytic asymmetric 1,4-addition is an essential process.[64] Many organocatalytic examples focus on the use of dialkylzinc reagents, with significant progress being made using a Cu(II) catalysis with phosphorous based chiral ligands.[65]

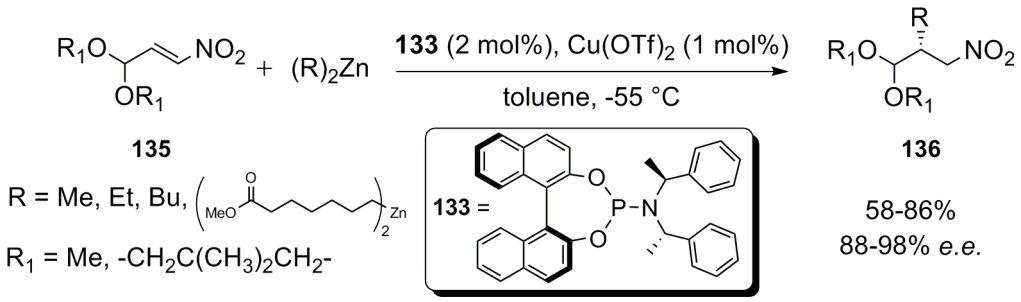
Use of the phosphoramidite ligand **133** originally developed by Feringa,[66] was further examined by Wendisch *et al*. in 1998.[67] Development of a catalytic conjugate addition of diethylzinc to substituted nitroalkene **132**, using $Cu(OTf)_2$ (2 mol%) and phosphoramidite ligand **133** (4 mol%) enabled the addition to proceed in quantitative yield, to afford **134** with high *e.e.* (86%) (Scheme 1.38). Unfortunately further

development using nitrostyrene, led to slightly lower conversion (90%) and enantioselectivity (48%).



Scheme 1.38: Catalytic enantioselective addition of diethylzinc.

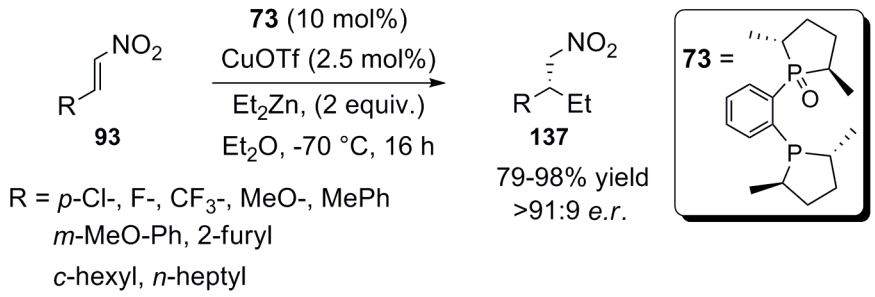
Feringa *et al.* have extensively studied the conjugate addition to α,β-unsaturated compounds, including nitroalkenes.[68] In particular, they have reported a large number of examples using dialkylzinc reagents, with the most recent published in 2003.[65] A variety of nitropropene acetals **135** were treated with 1.2 equivalents of simple dialkylzinc reagents with $Cu(OTf)_2$ and phosphoramidite **133** to produce the products **136** in excellent yield (58-86%) and enantioselectivities (88-98% *e.e.*) (Scheme 1.39). Further functionalisation *via* manipulation of the nitro group also allowed for synthesis of the corresponding aldehyde or acid.



Scheme 1.39: Phosphoramidite catalysed conjugate addition.

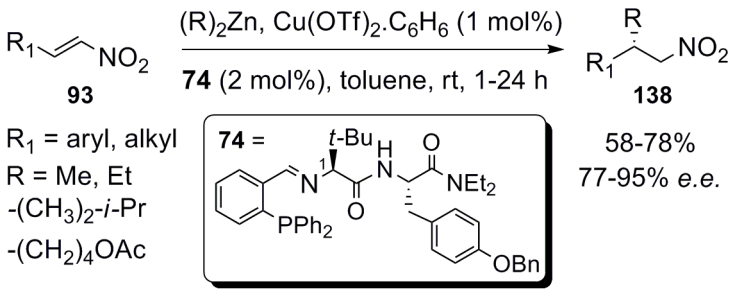
One of the most recent examples of dialkylzinc addition to nitroalkenes was reported by Charette *et al*.[69] This work investigated the application of the chiral bis(phosphine) monoxide ligand **73** for the enantioselective addition of dialkylzinc reagents. Optimsation found that the copper:ligand ratio was crucial in controlling the levels of enantio-induction with 10 mol% of phosphino ligand **73** and 2.5 mol% $Cu(OTf)_2$ proving both high yields and selectivities. Choice of solvent also had a significant effect on the reaction, with diethyl ether and toluene providing superior results. The

reaction was performed using a variety of aromatic and alkyl substituted nitroalkenes **93** to afford products **137** in excellent yield (70-98%) and *e.r.* (>91:9) (Scheme 1.40).



Scheme 1.40: bis(phosphine)monoxide catalysed conjugate addition.

Finally, Hoveyda *et al*. published the conjugate addition of dialkylzinc reagents to nitroalkenes using a chiral dipeptide phosphine ligand.[70] A screen of amino acid based ligands identified that ligands bearing two amide groups led to efficient and selective reactions. It was also noted that the presence of chirality at C-1 was also necessary for achieving high asymmetric induction. A large range of aromatic and alkyl substituted nitroalkenes were subjected to dialkylzinc reagents (mainly diethyl- and dimethylzinc) with 2 mol% of the peptide ligand **74** and $Cu(OTf)_2.C_6H_6$. This led to good yield (58-78%) and high *e.e.* (77-95%) of the desired conjugate addition products **138** (Scheme 1.41).

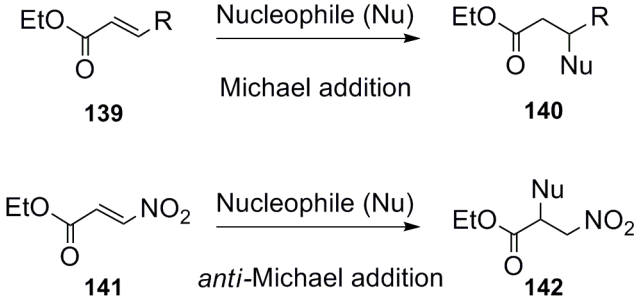


Scheme 1.41: Hoveyda's asymmetric dialkylzinc addition.

1.6.3 Conjugate Addition to Nitroacrylates

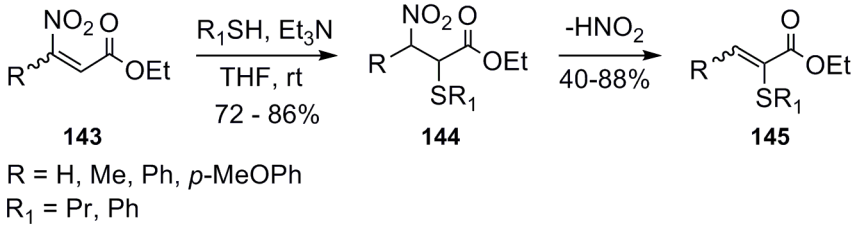
The conjugate addition of various nucleophiles to α,β-unsaturated alkenoates **139** in most cases occurs regioselectively at the β-position leading to addition products **140**. However, this regioselectivity can be successfully inverted by the installation of the highly electron-withdrawing nitro group, at the β carbon. This can lead to the

formation of the α-substituted product **142**, known as the *anti*-Michael addition product (Scheme 1.42).



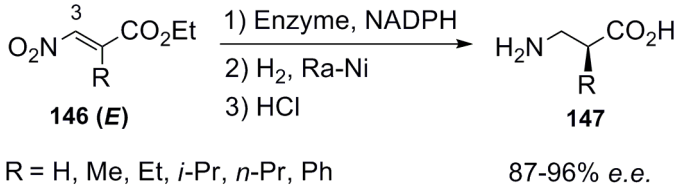
Scheme 1.42: α vs β conjugate addition to Michael acceptors.

This inversion in regioselectivity has led to extensive literature surrounding this area. In 2006, Lewanowska reported the nucleophilic addition to nitroacrylates in their synthesis of α-thioacrylates *via in situ* elimination of nitrous acid.[71] Treatment of nitroacrylates **143** with propanethiol or thiophenol in the presence of triethylamine (0.4 equivalents) provided the α-substituted products **144** in good to excellent yield as a 1:1 mixture of diastereoisomers. The authors also found that when using aliphatic nitroalkenes, the 1,4-addition products reacted further, causing elimination of nitrous acid and hence affording the desired α-thioacrylates **145** (Scheme 1.43).



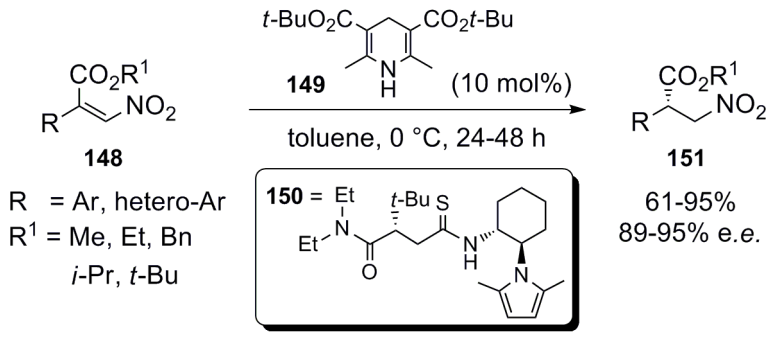
Scheme 1.43: α-Addition to nitroacrylates.

Also in 2006, Stewart *et al.*[72] developed an efficient route to β-aminoacids, *via* conjugate addition to nitroacrylates using the 'Sacharomyces carlsbergensis old yellow enzyme'. A variety of nitroacrylates **146** were synthesised and subjected to the enzyme with NADPH, to afford the corresponding addition products in 74-94% yield. Subsequent treatment with H_2 and Raney nickel allowed reduction of the nitro group in 75-85%. Finally, ester hydrolysis using HCl, afforded the desired β-aminoacids **147** isolated as the HCl salt in excellent yield (88-95%) and *e.e.* (87-96%) (Scheme 1.44). Unfortunately, development of the reaction with a substituent in the 3-position was unsuccessful, as the isolated products were essentially racemic.



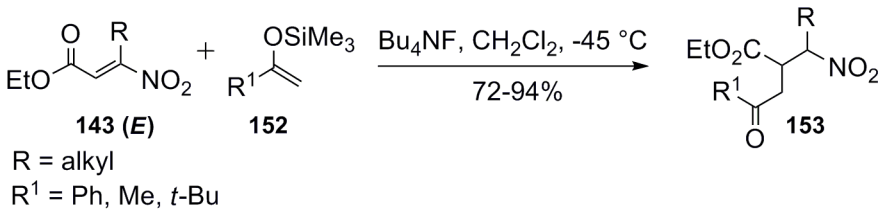
Scheme 1.44: Bioreduction of nitroacrylates.

Later in 2008, the List group published a complimentary approach to the synthesis of β-aminoacids **151** involving organocatalytic transfer hydrogenation of β-nitroacrylates **148**.[73] Treatment of the (*Z*)-nitroacrylate **148** with Hantzsch ester **149** and thiourea catalyst **150**, furnished the corresponding saturated ester **151** in good yield (61-95%) with high *e.e*. (89-95%). The reaction proved to be general and was successful when using a variety of ester substituents as well as aromatic and heteroaromatic substituents on the nitroalkene (Scheme 1.45).



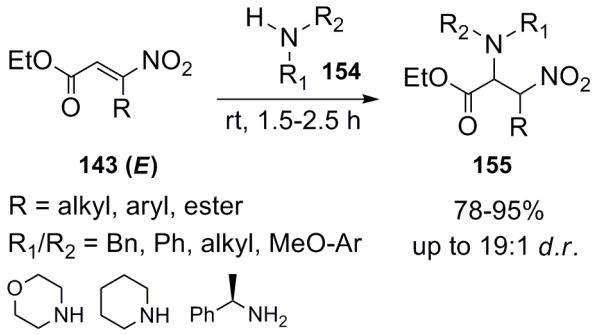
Scheme 1.45: Organocatalytic reduction of nitroacrylates **148**.

In addition to hydrogen transfer, the use of functionalised nucleophiles has been examined. Addition of silyl enol ethers **152** to nitroacrylates **143** was reported by Ballini and co-workers in 2008.[74] Unfortunately, the products **153** exhibited poor stereoselectivity, however these examples represent efficient methods for rapid increase in complexity from relatively simple starting materials (Scheme 1.46). Later, Ballini and co-workers expanded this work to incorporate the addition of malonate derivatives, using catalytic K_2CO_3. These reactions also proceeded in good yield, but with poor selectivity.[75]



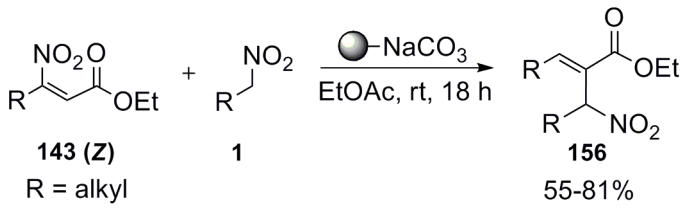
Scheme 1.46: Silyl enol ether addition to nitroacrylates.

The same group also published the *anti*-Michael addition of amines to nitroacrylates.[76] Reaction between amine **154** and nitroacrylate **143** (1:1) performed at room temperature under solvent and catalyst free conditions afforded the desired β-nitro-α-amino esters **155**. Scope of the reaction was examined using a variety of aliphatic and aromatic primary and secondary amines to furnish the aminoesters **155** in 78-95% yields. It was also demonstrated that when secondary amines were used, the diastereoselectivity in the nitroamine products was superior (up to 9:1) to when the reactions were performed using primary amines (Scheme 1.47).



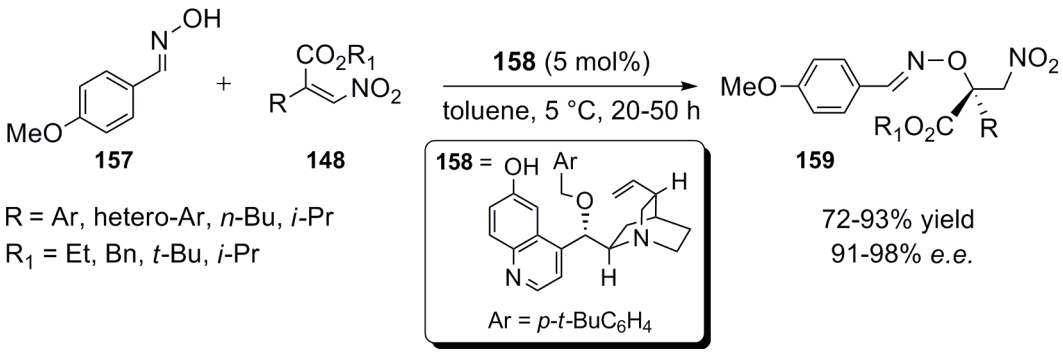
Scheme 1.47: Amine addition to nitroacrylates.

Ballini *et al.* further developed this research to perform conjugate addition under solid supported conditions.[77] The methodology was used for the development of a diastereoselective synthesis of nitro-functionalised α,β-unsaturated esters. Conjugate addition of nitroalkenes **1** to nitroacrylate **143** were carried out using a variety of basic solid promoters. The best results were achieved when using sodium carbonate on a polymer solid support. A variety of alkyl substituted nitroacrylates were utilised in the reaction, which proceeded *via* elimination of nitrous acid to form unsaturated esters **156** in high *d.r.* (>90%) and good yield (55-81%) as the *E* isomer (Scheme 1.48). It was noted that if the reaction was attempted with non-identical alkyl substituents on the nitroacrylate and nitroalkane, a mixture of elimination products were isolated.



Scheme 1.48: Solid supported addition of nitroalkanes.

Finally, during this research program, Chen and Xiao described an organocatalytic conjugate addition of oximes **157** to nitroacrylates **148** to yield amino acid derivatives using a cinchona alkaloid.[78] After extensive optimisation, cinchona alkaloid **158** was identified as a suitable catalyst to enable the reaction to be carried out with high selectivity. The process enabled the use of a large array of substituents on the nitroacrylate incorporating alkyl, aryl and heteroaryl groups to afford the products **159** in good yield (72-93%) and excellent *e.e.* (91-98%) (Scheme 1.49).



Scheme 1.49: Enantioselective addition of oxime **157** to nitroacrylates **148**.

A favourable transition state (**160**) for the reaction was proposed. It was postulated that activation of the electrophile could be performed by coordination of the phenol O-H group of catalyst **158** through hydrogen bonding interactions. It was suggested that this would lead to the oxime attacking the *Si* face of the nitroacrylate, forming the observed stereoisomer (Figure 1.5).

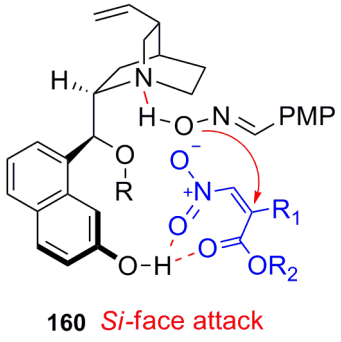
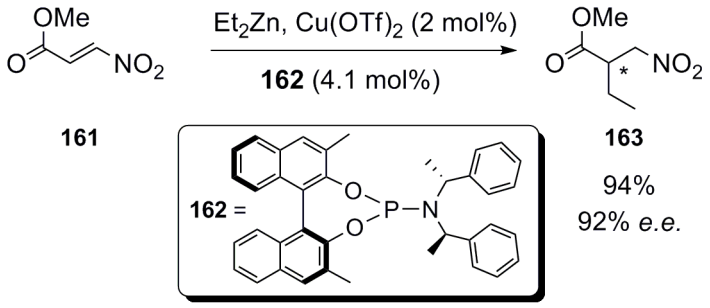


Figure 1.5: Proposed transition state for the conjugate addition.

Finally, Sewald *et al.* reported the first enantioselective synthesis of β-homo-aminoacids **163** using phosphoramidite ligands.[79] A number of phosphoramidites were examined using diethylzinc and activated nitroolefin, methyl 3-nitropropenoate **161**. Addition was found to be most successful when using phosphoramidite **162** (1.0 mol%), with $Cu(OTf)_2$ (0.5 mol%) in diethyl ether at -78 °C. This allowed the amino acid derivatives **163** to be isolated in 74-94% yield, with up to 92% *e.e.* (Scheme 1.50).



Scheme 1.50: Enantioselective diethylzinc addition.

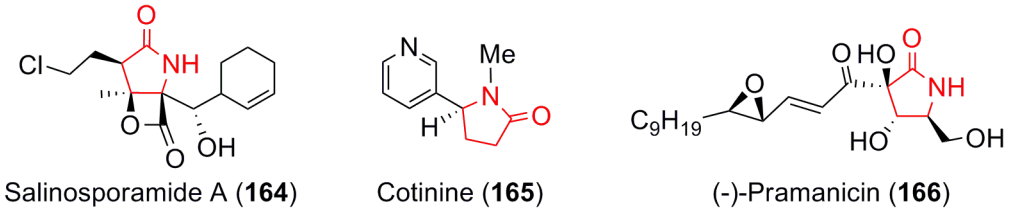
This section has highlighted the diverse scope and efficiency of the conjugate addition to nitroacrylates. This reaction is important due to the rapid synthesis of complex molecules *via* this method and is particularly significant for the development of the 1,4-addition/nitro-Mannnich/lactamisation reaction investigated during this research.

1.7 Stereoselective Synthesis of Pyrrolidinones

The 1,4-addition/nitro-Mannich reaction developed within the Anderson group,[36] has been expanded during this research to enable the synthesis of pyrrolidinone structures. This section will therefore discuss current synthetic methods for the synthesis of pyrrolidinones and significant examples related to tandem or cascade reactions.

The study of hetereocycles, including the pyrrolidinone structure is a significant area within organic chemistry. Heterocyclic compounds are present in an enormous quantity of naturally occurring compounds as well as unnatural, pharmaceutical and agrochemical compounds.[80] The pyrrolidinone structure itself is found in many natural occurring compounds including salinosporamide A (**164**), a marine natural product produced by the bacterium *Salinispora tropica*.[81] In addition, cotinine

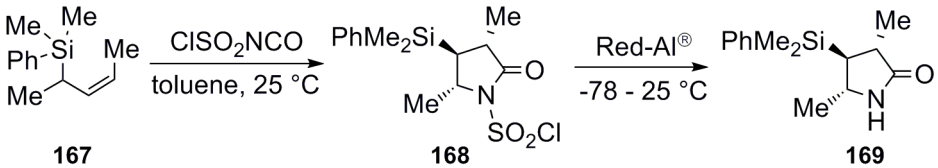
(**165**),[82] containing an *N*-methyl pyrrolidinone, is a metabolite of nicotine and is used as an indicator of tobacco smoke exposure. Finally, (-)-pramanicin (**166**) is a novel antimicrobial agent isolated from a fungus belonging to the *Stagonospora* species (Figure 1.6).[83]



Salinosporamide A (**164**) Cotinine (**165**) (-)-Pramanicin (**166**)

Figure 1.6: Pyrrolidinone containing compounds.

Due to their utility as building blocks in organic synthesis, widespread literature exists concerning the synthesis of the pyrrolidinone motif. In 1999, Woerpel *et al.* reported the [3+2] annulation of allylsilanes with chlorosulfonyl isocyanates to produce a stereoselective synthesis of 2-pyrrolidinones.[84] Treatment of α-substituted allylsilane **167** with chlorosulfonyl isocyanate, at room temperature in toluene afforded pyrrolidinone **168** *via* a formal [3+2] annulation. Pyrrolidinone **168** was found to be unstable, therefore direct reduction to remove the sulfone protecting group was performed using Red-Al® to yield the unprotected pyrrolidinones **169** in good yield (68% over two steps) (Scheme 1.51).



167 **168** **169**

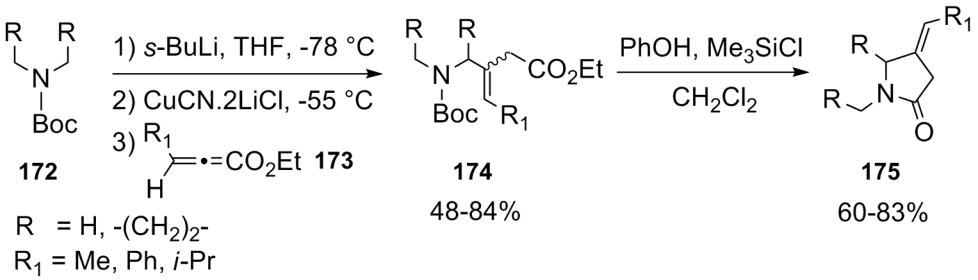
93:7 (*Z*:*E*) 68%, 92:8 *d.r.*

Scheme 1.51: Pyrrolidinone synthesis *via* [3+2] annulation.

Stereoselectivity could be determined by the geometry of the allylsilane substrate, hence when using *Z*-allylsilane **167** the relative stereochemistry of the product was opposite to when using the *E* isomer. It was postulated that the initial electrophilic attack was stereoselective and would occur *anti* peri planar to the silyl group to give intermediate **170**. It was suggested that the stereochemistry at C-3 would be set due to the alkene geometry of **167**. Subsequent 1,2-silyl migration would then provide intermediate **171**, which could undergo cyclisation *anti* to the silyl group, leading to the observed product **168** (Scheme 1.52).

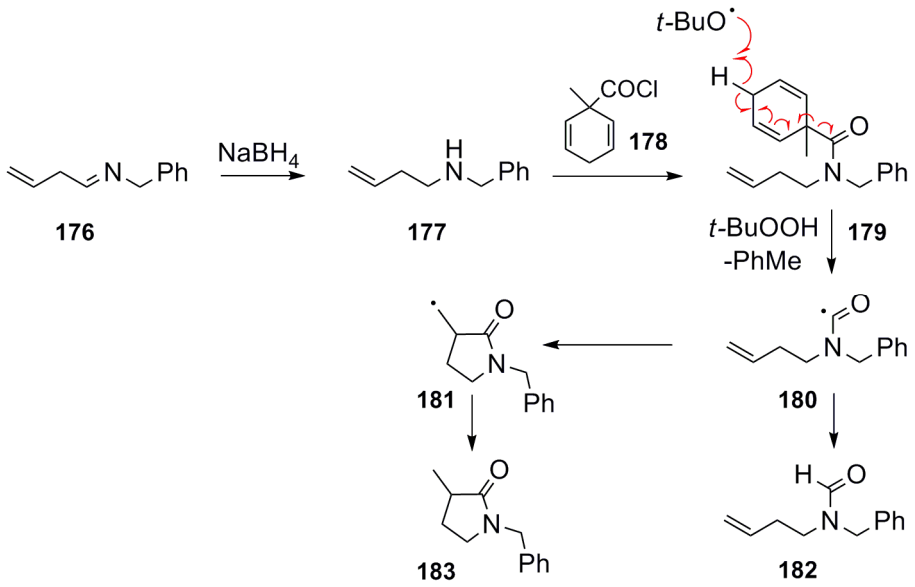
Scheme 1.52: Mechanistic analysis of pyrrolidinone formation.

The stereoselective synthesis of 4-alkylidene pyrrolidinones **175** was reported by Dieter *et al.* in 1999.[85] Conjugate addition of α-aminoalkylcuprate reagents (formed using **172**, *s*-butyllithium and CuCN.2LiCl) to allenyl esters **173** were performed successfully to afford intermediate **174** in 48-84% yield. Cleavage of the Boc group and subsequent lactamisation then furnished the desired pyrrolidinones **175** with good regiocontrol of the resulting olefin (Scheme 1.53).



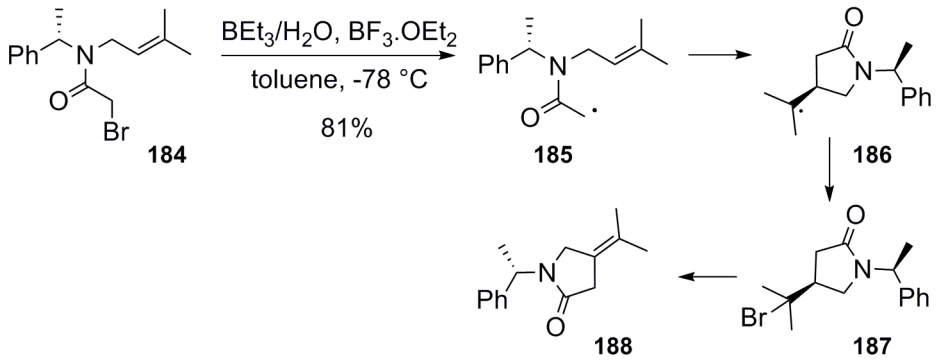
Scheme 1.53: Synthesis of alkylidene pyrrolidinones.

The use of radical cyclisations in the synthesis of pyrrolidinones is also ubiquitous. In 2000, Walton *et al.* developed a tin free homolytic route to β- and γ-lactams *via* the generation of an aminoacyl radical **180**.[86] Benzylimine **176** was reduced to the corresponding benzylamine **177** with sodium borohydride followed by reaction with acid chloride **178**. The resulting amide **179** was treated with radical initiator di-*tert*-butyl peroxide (DTBP), which promoted formation of radical aldehyde **180**. This allowed cyclisation to occur, hence affording the pyrrolidinone **183** in 53% yield. The authors attempted to study the reaction mechanism, using electron paramagnetic resonance spectroscopy, which successfully characterised the proposed radical intermediates **180** and **181**, providing good evidence that the reaction was proceeding *via* this pathway (Scheme 1.54).



Scheme 1.54: Radical initiated formation of γ-lactams.

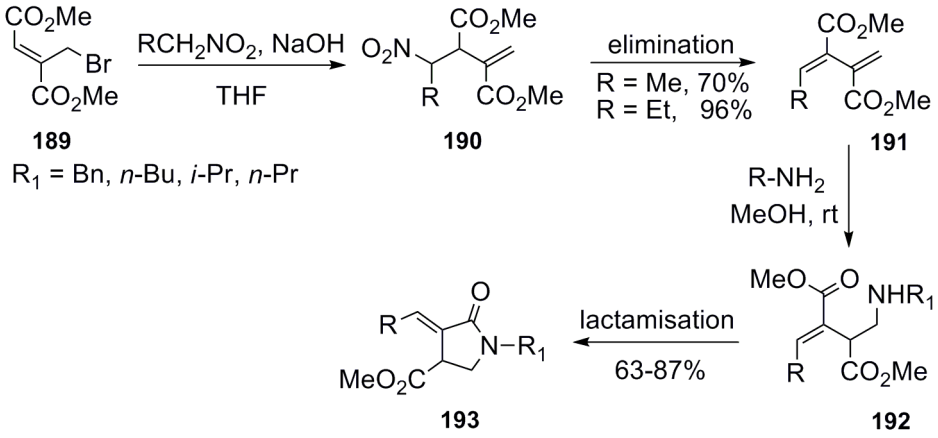
Sartillo-Piscil and co-workers reported the formation of the pyrrolidinone structure by use of a 5-*exo*-trig radical cyclisation mediated by $BF_3.OEt_2$.[87] Bromide **184** was treated with $BF_3.OEt_2$ and BEt_3/H_2O in toluene at –78 °C to yield the corresponding pyrrolidinone **188** in 81% yield. Formation of initial radical intermediate **185** was proposed, which could undergo cyclisation to give **186**. Bromine 'atom transfer' was then postulated, to afford bromide **187**, which could undergo elimination to yield the desired product **188** (Scheme 1.55).



Scheme 1.55: Radical mediated cyclisation to form pyrrolidinone **188**.

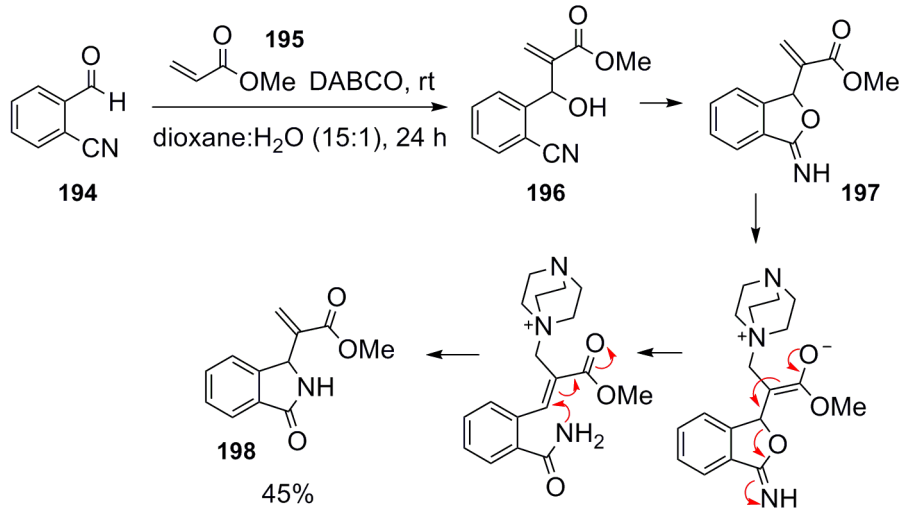
Among reports detailing pyrrolidinone synthesis in the literature, many focus on formation of the corresponding unsaturated analogues, including pyrrolidinones containing both *exo*- or *endo* alkenes. In 2001, Amri reported the stereospecific synthesis of α-alkylidene-γ-lactams, *via* a 1,3-butadiene intermediate **191**.[88] The pyrrolidinone products **193** had attracted significant attention due to their importance

as biologically active species.[89] Alkylation of allyl bromides **189** using a variety of nitroalkanes **1** in the presence of NaOH was carried out *via* SN_2' reaction to give intermediate **190**. Subsequent elimination of nitrous acid under the reaction conditions furnished diene **191** with 100% selectivity in favour of the *E* isomer. Reaction of diene **191** with primary amines *via* 1,4-addition to the α-β-unsaturated ester, followed by lactamisation of the resulting amine **192** formed the pyrrolidinone or γ-lactam products **193** in excellent yield (63-87%). Although this method details an efficient method for the synthesis of functionalised pyrrolidinones, the procedure suffers from a relatively lengthy route to the required structures (Scheme 1.56).



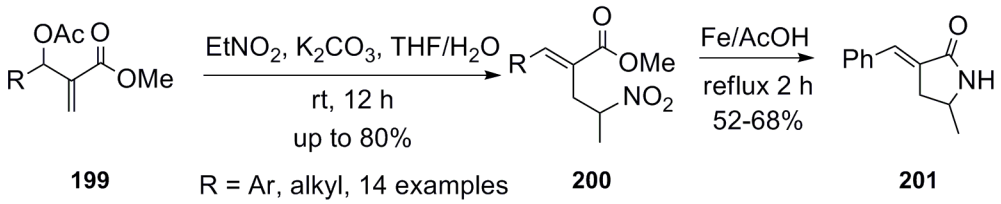
Scheme 1.56: Stereospecific route to α-alkylidene-γ-lactams.

The Baylis-Hillman reaction, is an important, atom economic carbon-carbon bond forming reaction within organic synthesis and has therefore been utilised in the formation of pyrrolidinones. In 2003, Lee *et al.*[90] reported the synthesis of dihydroindoles **198** as a by-product of the reaction between 2-cyanobenzaldehyde **194** with methyl acrylate **195** in the presence of sub-stoichiometric amounts of DABCO. The authors reported that instead of the expected benzofuran structure **197**, the rearrangement product **198** was observed in 45% yield. This methodology was then extended to a variety of acrylates however only yields in the range 33-45% were obtained (Scheme 1.57).



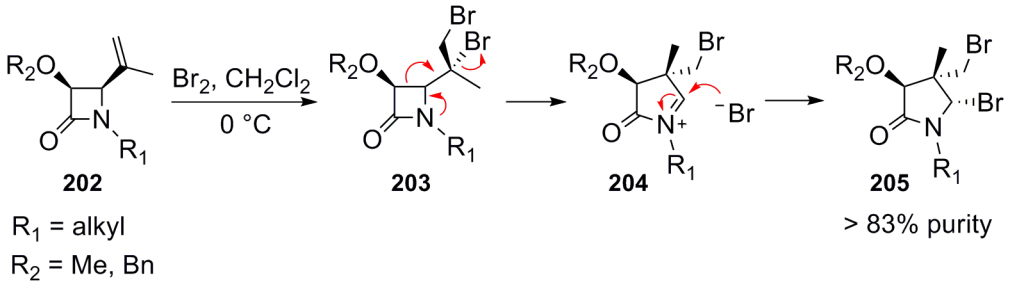
Scheme 1.57: Pyrrolidinone compounds *via* Baylis-Hillman reaction.

A further application of the Baylis-Hillman reaction was reported by Basavaiah.[91] Treatment of Baylis-Hillman acetates **199** with nitroethane or nitromethane in the presence of K_2CO_3 in THF/H_2O at room temperature afforded trisubstituted alkenes **200**. Subsequent nitro-reduction using Fe/AcOH allowed cyclisation to proceed smoothly to provided *exo*-methylene-pyrrolidinones **201** in 52-68% yield (Scheme 1.58).



Scheme 1.58: Baylis-Hillman acetates in pyrrolidinone formation.

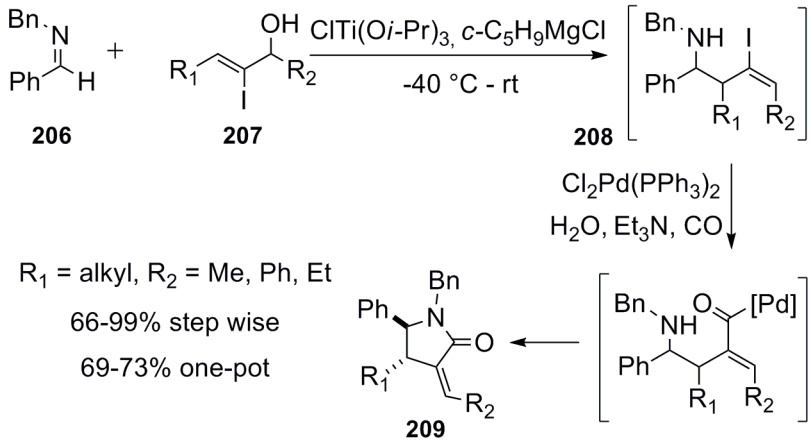
One further transformation that has been utilised in the synthesis of pyrrolidinone structures are ring expansion and contraction reactions. De Kimpe *et al*.[92] reported an electrophile induced ring expansion of β-lactams to afford the corresponding γ-lactam or pyrrolidinone. β-lactams **202** were treated with bromine (1 equivalent) in CH_2Cl_2 to afford bromide **203**, followed by ring opening to give intermediate **204**. Finally, further bromination afforded the pyrrolidinones **205** as a single diastereoisomer. Unfortunately, the products (**205**) were found to be unstable to purification and only the purity (>83%) was quoted. This methodology was then extended to the use of other nucleophiles such as H_2O and $TMSN_3$ to furnish the corresponding pyrrolidinones in good yield (43-87%) (Scheme 1.59).



Scheme 1.59: Ring expansion to form pyrrolidinone structures.

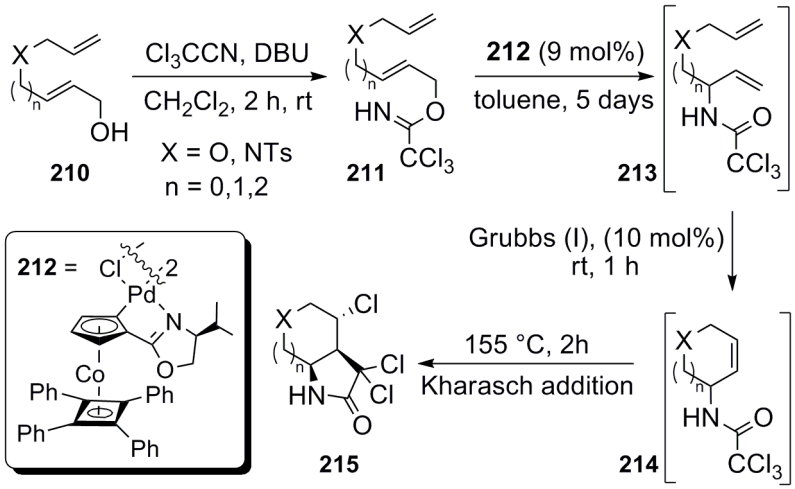
1.8 Tandem Processes for the Synthesis of Pyrrolidinones

As described in the previous section, the synthesis of *exo*-alkylidene-γ-lactams has been reported extensively in the literature. In 2009, Micalizio developed this methodology further to report a convergent one pot reductive cross-coupling, carbonylation reaction.[93] Previous studies had developed a highly diastereoselective titanium mediated coupling of allylic alcohols with imines.[94] Examining this further led to the installation of a halogen at the two-position of the allylic alcohol, enabling further reaction using palladium catalysed carbonylation chemistry. Treatment of *N*-benzyl protected imine **206** with iodide **207** allowed efficient coupling to give intermediate **208**. This was followed by reaction with $Cl_2Pd(PPh_3)_2$, Et_3N and CO, to furnish the desired lactams **209**. Reactions were carried out between aromatic substituted benzyl protected imines and cyclic or acyclic allylic alcohols to afford the corresponding pyrrolidinones **209** in good yield (66-99%) and excellent selectivity (>20:1) (Scheme 1.60).



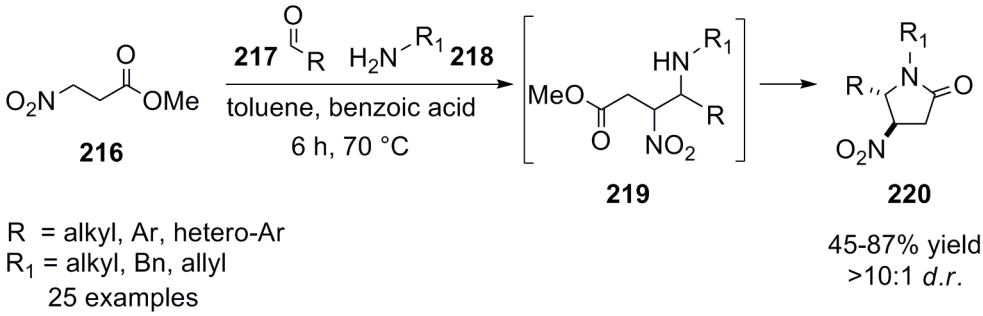
Scheme 1.60: One-pot reduction cross coupling/carbonylation reaction.

More recently, a tandem three-step process for the synthesis of bicyclic γ-lactams has been reported.[95] This involved use of allylic trichloroacetimidates **211** to carry out palladium(II) mediated Overman rearrangement followed by treatment with Grubb's first generation complex to catalyse both a ring closing metathesis reaction and Kharasch cyclisation. Allylic alcohols **210** was converted to the corresponding allylic trichloroacetimidates **211** using trichloroacetonitrile and sub-stoichiometric quantities of DBU. Without purification, the products were subjected to the Overman rearrangement using bis(acetonitrile)palladium(II) chloride (10 mol%) to afford intermediate **213**. Grubb's (I) catalyst (10 mol%) was added and the reaction heated to 60 °C to furnish intermediate **214**. The temperature was then increased to 155 °C to initiate Kharasch cyclisation, which led to isolation of the bicyclic lactams **215**, as a single diastereoisomer in 52-87% yield. The authors proceeded to develop an enantioselective version of this reaction using the commercially available (*S*)-COP-Cl ligand **212**, which led to high *e.e.* (89-94%) of the bicylic products **215** (Scheme 1.61).



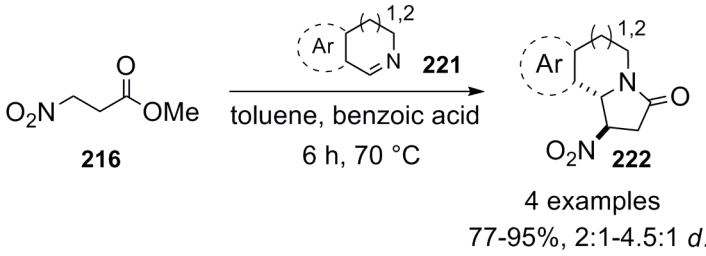
Scheme 1.61: Tandem rearrangement/metathesis/cyclisation reaction.

Finally, during this research program, Dixon and co-workers published a nitro-Mannich/lactamisation cascade for the synthesis of pyrrolidin-2-ones.[96] Their strategy involved treatment of aldehydes **217** with amines **218** leading to the formation of the corresponding imine *in situ*. Proton exchange with acidic nitroalkane **216** followed by carbon-carbon bond formation achieved *via* nitro-Mannich reaction, furnished intermediate **219**. Final lactamisation then afforded the desired cyclic products **220** in good yield (45-87%) and excellent *d.r.* (>10:1) (Scheme 1.62).



Scheme 1.62: Formation of pyrrolidinones **220** *via* nitro-Mannich reaction.

The scope of the reaction was investigated with respect to the amine and aldehyde to afford a wide range of analogues in good yield (45-87%) and diastereoselectivities, (>10:1) in favour of the *anti* configuration. Extension of this work enabled the reaction to be performed using cyclic imines **221**, to furnish the polycyclic products **222** in excellent yield (77-95%) and moderate diastereoselectivities (2:1-4.5:1) (Scheme 1.63).

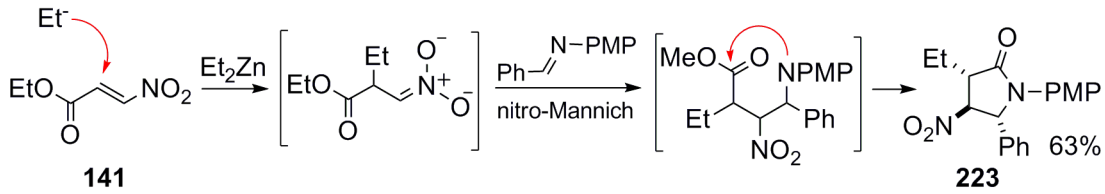


Scheme 1.63: Synthesis of polycyclic pyrrolidin-2-ones.

Although a large number of reports exist in the literature describing the efficient synthesis of the pyrrolidinone structure, many involve lengthy procedures to obtain the appropriate starting materials. In addition, whilst some reports have demonstrated highly diastereoselective procedures, few have developed methodology to synthesise the structures in an enantioselective manner. This information indicates that an efficient, stereoselective synthesis of highly functionalised pyrrolidinones using the 1,4-addition/nitro-Mannich/lactamisation reaction described in this thesis, would be extremely useful for the formation of the pyrrolidinone structure in heterocyclic and synthetic organic chemistry.

2.0 Proposed Research

This research aimed to generate an efficient synthesis of pyrrolidinones using the nitro-Mannich reaction. The project built upon work within the Anderson group, involving the development of a tandem 1,4-addition/nitro-Mannich procedure.[36] During these studies, it was found that when carrying out the 1,4-addition/nitro-Mannich reaction using nitroacrylate **141**, further *in situ* lactamisation occurred, to form the corresponding pyrrolidinone **223** as a single diastereoisomer (Scheme 2.0).[97]



141 **223**

Scheme 2.0: Pathway to pyrrolidinone formation.

With this result in hand, the initial challenge during this research was to optimise and expand this methodology to develop a general, efficient 1,4-addition/nitro-Mannich/lactamisation reaction. This would require investigation of the scope with respect to the imine substituent, with aromatic, alkyl and cyclic imines being examined. Alternative nucleophiles for the 1,4-addition reaction would also be explored, as well as choice of nitrogen protecting groups.

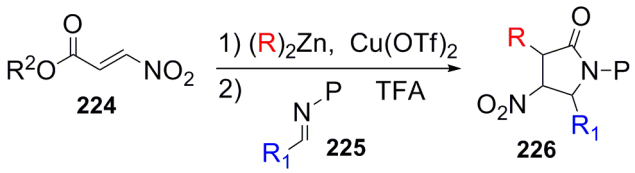
Development of an asymmetric variant of this reaction would also be attempted, with investigations focusing on the use of a suitable ligand/catalyst system to allow the reaction to be performed enantioselectively. Studies into the origin of the remarkable stereoselectivity observed in this reaction would also be carried out, as well as work towards the formation of additional heterocyclic structures *via* this method. This expedient route to pyrrolidinones would demonstrate both the synthetic utility of the 1,4-addition reaction, as well as the advantages of using this methodology in the nitro-Mannich reaction. In addition, further functionalisation of the pyrrolidinones could lead to practical building blocks for use in synthesis.

3.0 Results and Discussion

The development of tandem or cascade reactions in organic synthesis has rapidly expanded in recent years.[98] These processes allow for the expedient synthesis of functionalised chiral molecules from simple achiral precursors. Reaction processes of this type can generate highly efficient reactions without the need for time-consuming work-up and purification procedures. This section will describe the results obtained towards the development of the proposed 1,4-addition/nitro-Mannich/lactamisation reaction to produce pyrrolidinones.

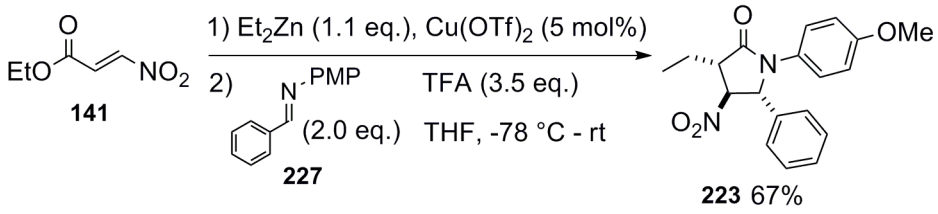
3.1 Initial Result

Following previous work within the Anderson group (see section 1.0),[36] attention was turned to the development of a tandem 1,4-addition/nitro-Mannich/lactamisation reaction. It was postulated that when utilising nitroacrylates **224**, with a variety of dialkylzinc reagents and substituted imines **225**, the β-nitroamine product resulting from the 1,4-addition/nitro-Mannich reaction would react further by *in situ* cyclisation, to form a range of highly substituted pyrrolidinones **226** (Scheme 3.0).



Scheme 3.0: Proposed pathway to pyrrolidinones **226**.

With this in mind, ethyl nitroacrylate **141** was treated with $Cu(OTf)_2$ and diethylzinc at –78 °C, followed by warming to room temperature. When the 1,4-addition reaction was complete (TLC analysis), PMP imine **227** derived from benzaldehyde and TFA were added at –78 °C in order to carry out the *in situ* nitro-Mannich and lactamisation reactions consecutively. As anticipated, warming to room temperature followed by aqueous work up afforded the desired pyrrolidinone **223** in 45% yield as a single diastereoisomer (Scheme 3.1).[99]



Scheme 3.1: One-pot formation of pyrrolidinone **223**.

The choice of diethylzinc in this initial study was due to previous success within the Anderson group, using dialkylzinc reagents.[36] In addition, the asymmetric 1,4-addition to nitroalkenes using this type of reagent is known (see section 1.6), which could allow the development of an asymmetric variant of the pyrrolidinone formation at a later stage. The initial use of *N*-PMP protection on the imine partner was also due to previous work within the group,[36] however further studies into the effects of alternative *N*-protecting groups on the new three-step reaction would be required. Overall, this was a very promising result, allowing for further examination of the reaction. With this in mind, this reaction (Scheme 3.1) was used as a model system for optimisation of the reaction conditions.

3.2 Optimisation

With the initial result in hand, optimisation to create a viable process, which could be applicable to a range of substrates was explored. The first parameter under investigation was the equivalents of imine required for the nitro-Mannich reaction. Previous studies had used two equivalents of PMP-protected imine **227**, as this was found to be superior in achieving optimum diastereoselectivity in the nitro-Mannich reaction.[36] In this case however, only a single diastereoisomer has been isolated therefore it was postulated that the equivalents of imine could be reduced (Table 3.0).

Use of a Brønsted acid was also examined. Previous studies found that 3.5 equivalents of TFA (1.5 equivalents more than the equivalents of imine) were required for the reaction. It was therefore suggested that reduction of the imine **227** could in turn allow a reduction in the equivalents of TFA. When using just 1.1 equivalents of imine **227** and 2.6 equivalents of TFA, the yield increased to 52% (Table 3.0, Entry 2). Reduction of excess imine **227** in the crude reaction mixture also allowed for a more straightforward purification procedure. The temperature of the reaction remained unchanged during optimisation due to previous success when carrying out the reaction at –78 °C followed by warming to room temperature.

Heating the reaction to 40 °C after the addition of imine **227** and TFA was attempted, however this did not affect the isolated yield.

Reaction times were then assessed. Initial conditions required addition of the dialkylzinc reagent at –78 °C followed by warming to room temperature after 10 minutes. This was stirred at room temperature for 90 minutes before being re-cooled to –78 °C and imine **227** and TFA were added. The reaction mixture was subsequently held at –78 °C for two hours followed by further warming to room temperature for four hours. To obtain optimum conditions for this reaction, the time for each part of the tandem process had to be considered individually.

To ensure completion of the 1,4-addition reaction, the reaction time at room temperature was increased from 90 minutes to 15 hours before the addition of imine. This gave a slight decrease in yield (57%, Table 3.0, Entry 3), indicating that the initial 90 minutes was sufficient for complete conversion to the desired nitronate intermediate. Previously, it was found that keeping the reaction at –78 °C for two hours after the addition of imine **227** was optimum for achieving the best diastereoselectivity. However, as only one pyrrolidinone isomer was observed in this reaction, it was suggested that this could be decreased. When decreasing the time at –78 °C to just 10 minutes, a lower yield was seen (Table 3.0, Entry 4) however when leaving at –78 °C for 1 hour, a high yield of 64% was achieved (Table 3.0, Entry 5). Increasing the reaction time after the addition of imine from 4 hours at room temperature to 15 hours also led to an improved yield of 65% (Table 3.0, Entry 6). This indicated that pyrrolidinone formation was occurring gradually over time and a longer reaction time was required to gain higher isolated yields of the desired product.

Entry	Time (h)[a]	Time (h)[b]	Time (h)[c]	Equiv. Imine (227)	Equiv. TFA	Yield (%)
1	1.5	2.0	4.0	2.0	3.5	45
2	1.5	2.0	4.0	1.1	2.6	52
3	15	1.0	15	1.1	2.6	57
4	1.5	0.2	15	1.1	2.6	53
5	1.5	1.0	15	1.1	2.6	64
6	1.5	1.0	15	1.1	2.6	65

[a] Reaction time at room temperature after addition of dialkylzinc reagent.
[b] Reaction time at –78 °C after the addition of imine **227** and TFA.
[c] Reaction time at room temperature after the addition of all reagents.
All reactions carried out using Et_2O as the solvent.

Table 3.0: Optimisation of reaction conditions.

With the above results in hand, attention was turned to a solvent screen (Table 3.1). Using the developed conditions, toluene was used in place of Et_2O, which resulted in a significant decrease in yield to 25% (Table 3.1, Entry 1). In addition, use of CH_2Cl_2 reduced the yield to just 18% (Table 3.1, Entry 2). When using EtCN, TLC analysis showed initial formation of the nitronate took a further three hours, (90 minutes in Et_2O) and resulted in a moderate 49% (Table 3.1, Entry 3). Finally, the use of THF resulted in an excellent 66% (Table 3.1, Entry 4), equalling the yield obtained with Et_2O (Table 3.1, Entry 5), indicating that the reaction proceeded best in polar aprotic solvents.

Entry	Solvent	Yield (%)
1	Toluene	25
2	CH_2Cl_2	18
3	EtCN	49
4	THF	66
5	Et_2O	65

Table 3.1: Solvent screen for the one pot reaction.

Attention was then turned to varying the *N*-protecting group on the imine partner. When replacing the PMP protection with an OMB group, the nitro-Mannich/lactamisation proceeded well, however a decreased yield of 57% of the pyrrolidinone **228** was obtained (Table 3.2, Entry 1). This proceedure was also carried out using acetic acid in place of TFA, but resulted in a lower 37% yield. For this reason, all remaining experiments were carried out using TFA.

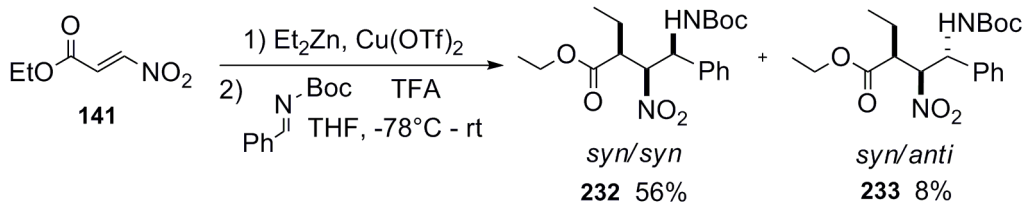
The use of *n*-butyl protected imine afforded pyrrolidinone **229** in a moderate 46% yield (Table 3.2, Entry 2), illustrating the ability of this reaction to tolerate alkyl as well as aryl substituents at this position. For the purposes of this study however, removal of the *N*-protecting group would be required after the reaction, to allow for further functionalisation of the pyrrolidinone. Use of the corresponding benzyl protected imine partner also gave a low yield of the pyrrolidinone **230** in 32% (Table 3.2, Entry 3). When using an *N*-protected allyl imine, the reaction proceeded to afford 50% of a 2.5:1 mixture of pyrrolidinone **231** and the corresponding acyclic β-nitroamine (Table 3.2, Entry 4). This study showed that in fact the original PMP *N*-protection was superior in achieving the highest yield for this reaction (Table 3.2, Entry 5).

Entry	Pyrrolidinone	*N*-Protection	Yield (%)
1	**228**	OMB	57
2	**229**	*n*-butyl	46
3	**230**	benzyl	32
4	**231**	allyl	36[a]
5	**223**	PMP	67

[a] Yield calculated by ^{1}H NMR. Isolated as a 2.5:1 mixture of pyrrolidinone and acyclic β-nitroamine respectively.

Table 3.2: Variation of *N*-protecting groups.

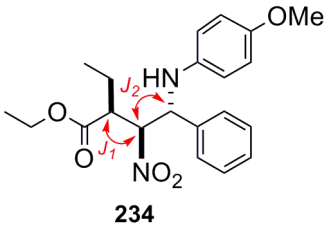
Finally, the reaction was performed using *N*-Boc protected imine, derived from benzaldehyde. In this case, none of the desired pyrrolidinone was observed, however two diastereoisomers of the acyclic β-nitroamine product were isolated. The compounds were separated by flash column chromatography to give **232** and **233** in 56% and 8% yields respectively (Scheme 3.2). This result suggests that due to the electron withdrawing nature of the Boc group, the nitrogen lone pair is less nucleophilic and therefore less likely to cyclise to form the pyrrolidinone in this case.



Scheme 3.2: Isolation of *N*-Boc protected β-nitroamines.

The relative stereochemistry of these products has been tentatively assigned by comparison of ^{1}H NMR coupling constants and with **234** (previously synthesised). Nitroamine **234** was isolated during previous work, which investigated the scope of the 1,4-addition-nitro-Mannich reaction on a variety of substituted nitroalkenes.[100] Isolation of **234** was carried out by quenching the reaction 5 minutes after warming from –78 °C, before cyclisation to the pyrrolidinone **223** could occur. This has enabled comparison of acyclic β-nitroamine **234** with Boc protected acyclic products **232** and **233**. During previous studies on the 1,4-addition/nitro-Mannich reaction,

two major diastereoisomers were isolated in varying ratios depending on the reaction conditions.[100] The relative stereochemistry across the three newly generated stereocentres was assigned as *syn/syn* and *syn/anti* therefore it has been assumed that these would also be the major products in the new three step 1,4-addition/nitro-Mannich/lactamisation reaction (Figure 3.0).



234

Entry	Compound	J_1 (Hz)	J_2 (Hz)
1	**232** (*syn*/*syn*)	9.6	9.3
2	**233** (*syn*/*anti*)	11.2	3.7
3	**234** (*syn/anti*)	10.5	5.0

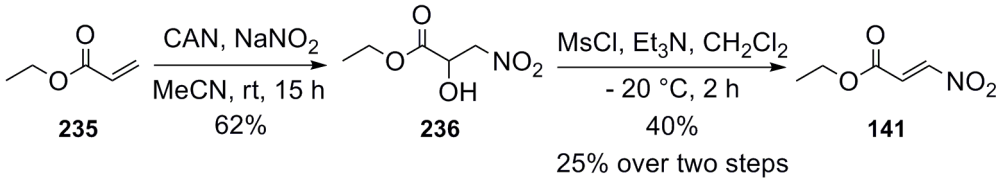
Figure 3.0: Comparison of ^{1}H NMR coupling constants.

Comparison of ^{1}H NMR coupling constants J_1 (C*H*Et – C*H*NO_2) and J_2 (C*H*NO_2 – C*H*Ph) for both isolated diastereoisomers **232** and **233** with previously synthesised **234**,[100] indicate that the minor diastereoisomer **233** has the same relative stereochemistry as **234** (*syn/anti*) and therefore by process of elimination, the major product **232** can be tentatively assigned as the *syn/syn* product.

The investigation into alternative *N*-protecting groups has shown that the original PMP protection is the most efficient for this reaction. The study has also demonstrated the ability of the reaction to tolerate a range of groups in this position, which could be applicable to a variety of synthetic applications.

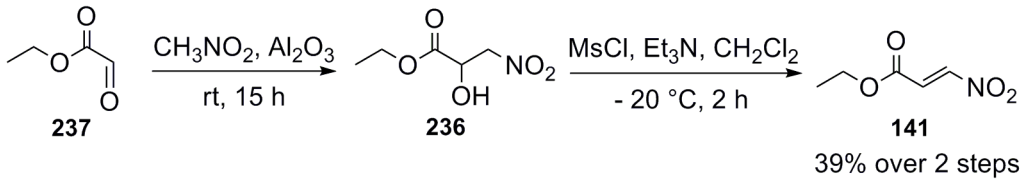
3.3 Reaction Scope

With optimised conditions in hand, investigation into the scope of the tandem reaction was required. For this purpose, preparation of large quantities of the starting material nitroacrylate **141** were required. Initial studies focussed on treatment of ethyl acrylate **235** with sodium nitrite to give intermediate nitroalcohol **236**. Dehydration to the desired nitroalkene was achieved by treatment with mesyl chloride and triethylamine to furnish nitroacrylate **141** in 25% over two steps (Scheme 3.3).



Scheme 3.3: Formation of nitroacrylate **141**.

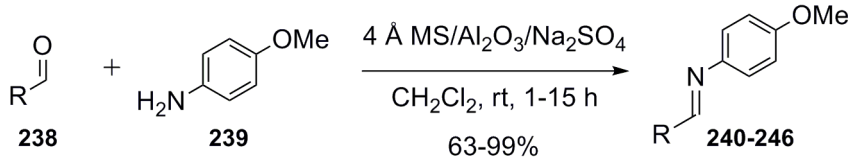
Although this represented a reasonable route to the desired nitroalkene, the low yielding reactions led us to consider alternatives. Use of the Henry reaction,[2] using ethylglyoxylate in nitromethane to afford **236**, produced a much cleaner crude reaction mixture, which could be used directly in the dehydration reaction (39% over two steps) (Scheme 3.4).



Scheme 3.4: Alternative route to nitroacrylate **141**.

Unfortunately, dehydration to afford **141** was consistently low yielding. This process was also attempted using acetic anhydride, however, no improvement was seen.[101] Although only a moderate yield of the nitroalkene **141** was obtained, this route provided a viable method to produce the gram quantities of material required for our reaction studies.

A range of imines were also synthesised for use within the tandem reaction. These were prepared *via* simple condensation of the corresponding aldehydes **238** and *p*-anisidine **239**, using a suitable drying agent (Table 3.3). The majority of reactions were stirred for 15 hours at room temperature before isolation, with the exception of ester **244**, which was stirred at 0 °C for 1 hour. Compounds isolated as a solid were purified by recrystallisation and were stable for a number of weeks at –20 °C. Compounds isolated as oils were used directly without further purification.

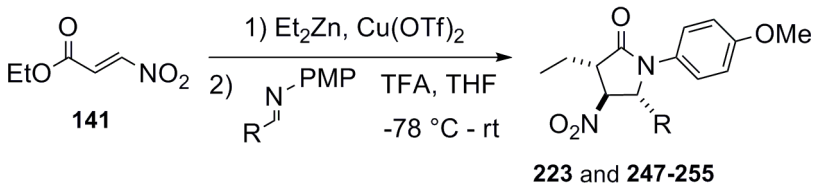


Entry	Imine	R	Yield (%)
1	**240**	2-tol	63
2	**241**	4-NO_2-Ph	88
3	**242**	4-CF_3-Ph	88
4	**243**	4-MeO-Ph	88
5	**244**	CO_2Et	98
6	**245**	2-MeO-Ph	94
7	**246**	3,5-Cl-Ph	99

Table 3.3: Synthesis of imines.

With starting materials in hand, the 1,4-addition/nitro-Mannich/lactamisation reaction was carried out on a range of imine substrates, using the optimised conditions. Aromatic groups with substituents in the *meta*- and *para*-positions proceeded well affording a single diastereoisomer in each case, as well as excellent isolated yields for the three step reaction (Table 3.4, Entries 1-7). Compounds with substituents in the *ortho*-positions gave slightly lower yields, possibly due to the increased steric bulk around the newly formed ring (Entries 8-10).

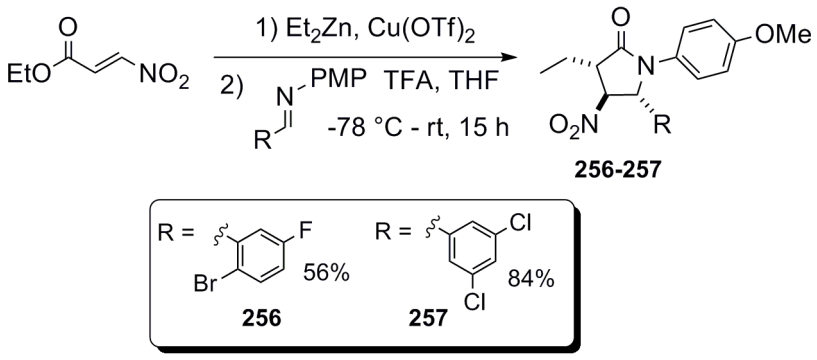
In all cases, the presence of an electron-withdrawing group afforded excellent yields of the corresponding pyrrolidinones (Table 3.4). It was suggested that increased electrophilicity of the imine, could promote the nitro-Mannich reaction, leading to higher isolated yields. In turn, electron-donating groups could reduce the electrophilicity at the imine centre therefore explaining the slight reduction in yield.



Entry	R	Yield (%)	Pyrrolidinone
1	Ph	67	**223**
2	4-tol	60	**247**
3	4-NO_2-Ph	58	**248**
4	4-CF_3-Ph	70	**249**
5	4-OMe-Ph	46	**250**
6	4-Cl-Ph	74	**251**
7	3-tol	72	**252**
8	2-tol	46	**253**
9	2-Br-Ph	56	**254**
10	2-MeO-Ph	49	**255**

Table 3.4: Variation of aromatic substituents.

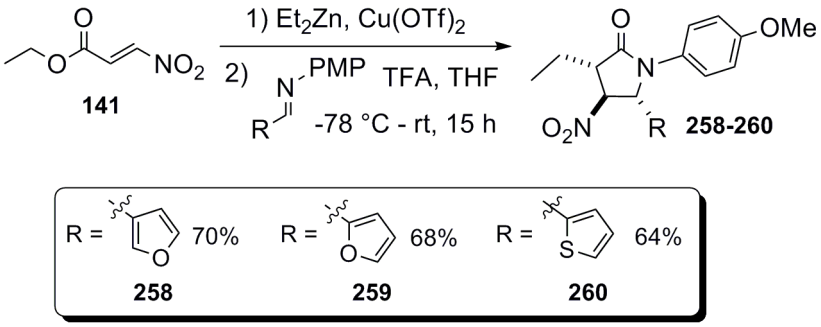
Success was also found when using imines with disubstituted aromatic groups. Reaction with 2-bromo-4-fluoro phenyl imine formed the pyrrolidinone **256** in good yield (56%) despite the presence of a sterically bulky *ortho*-bromine substituent. In addition, when using the electron-withdrawing 3,5-dichlorophenyl imine **246**, the reaction proceeded to afford pyrrolidinone **257** with an excellent 84% yield. (Scheme 3.5).



Scheme 3.5: Pyrrolidinones bearing an aromatic ring with two substituents.

The next area under investigation was the synthesis of analogues bearing a heterocyclic moiety. Imines derived from thiophene-2-carboxaldehyde, as well as 2-

and 3-furyl carboxaldehyde were used in the reaction to give excellent yields of the corresponding pyrrolidinones (Scheme 3.6).



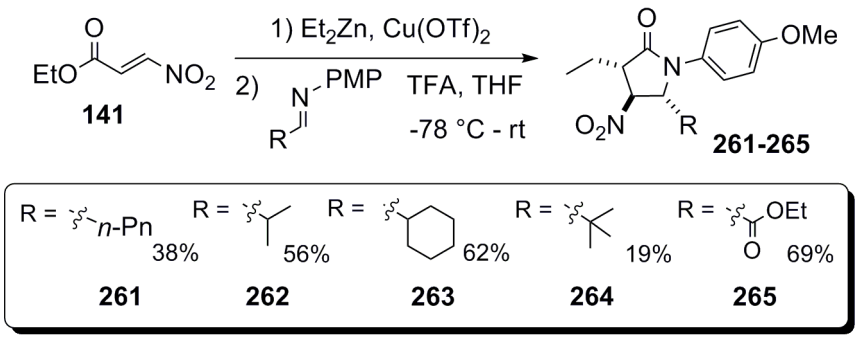
Scheme 3.6: Heterocyclic pyrrolidinones.

This study had proven the tandem 1,4-addition/nitro-Mannich/lactamisation reaction to work extremely well for imines bearing an aromatic group. The reaction had been shown to tolerate a large variety of substituents and all pyrrolidinones were isolated in good to excellent yields as a single diastereoisomer. With this in hand, incorporation of alkyl substituents was required.

Imines derived from cyclohexane carboxaldehyde, isobutyraldehyde, pivaldehyde and *n*-hexanal were used in the reaction. It is known that the instability of these imines towards tautomerisation to the corresponding enamine, can be problematic. This was particularly prevalent in the case of the *n*-pentyl imine, which is unstable even at –20 ° C overnight. For this reason, the material was freshly prepared and used directly in the tandem reaction to give pyrrolidinone **261** in 38%. The corresponding cyclohexyl- and isopropyl reactions also proceeded smoothly to afford pyrrolidinones **262**-**263** in good yield (Scheme 3.7). In contrast, reaction using the corresponding *t*-butyl imine gave a very low yield of 19% of the pyrrolidinone **264** along with 1,4-addition product and traces of the corresponding acyclic β-nitroamine. It was postulated that this imine was too sterically hindered to undergo the desired *in situ* nitro-Mannich reaction, which would account for the low conversion in this reaction. This reaction was also carried out by refluxing in THF, however no improvement in conversion to the nitro-Mannich product or isolated yield was observed (Scheme 3.7).

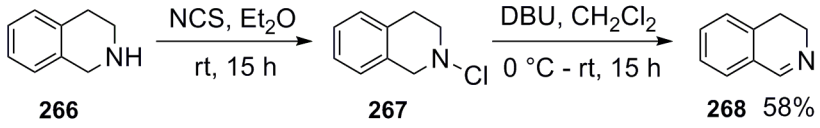
In addition to simple alkyl groups, an ester substituted imine derived from ethyl-glyoxylate, was used in the three step reaction to afford pyrrolidinone **265**. The reaction proceeded in excellent 69% yield and represents a concise synthesis of

proline derivatives, as well as an excellent opportunity for further functionalisation (Scheme 3.7).



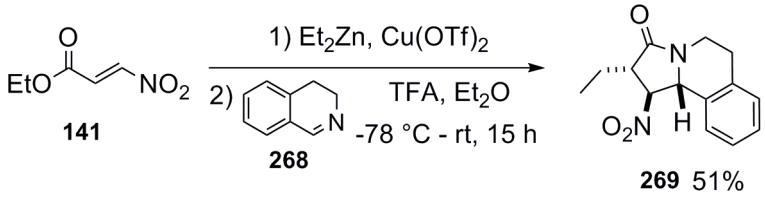
Scheme 3.7: Synthesis of alkyl substituted pyrrolidinones.

To further examine the scope of the tandem reaction, cyclic imines were also considered. To this end, synthesis of a simple cyclic imine bearing a stabilising aromatic ring, was carried out according to literature procedures.[102] Tetrahydroisoquinoline **266** was treated with NCS in Et_2O to give chloro-tetrahydroisoquinoline **267**, which was in turn treated with DBU to afford dihydroisoquinoline **268** in 58% over two steps (Scheme 3.8).



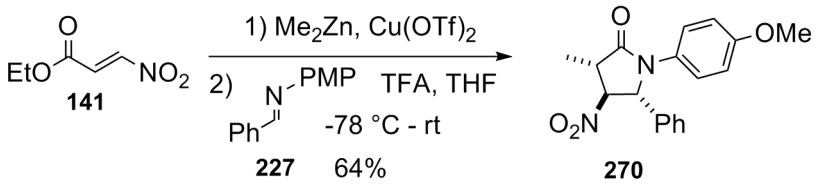
Scheme 3.8: Synthesis of cyclic imine **268**.

The one pot process was carried out utilising the cyclic imine **268**. The reaction proceeded as expected to give the pyrrolidinone **269** as a 5:1 crude mixture of diastereoisomers. The major diastereoisomer was isolated by flash column chromatography in 51% yield and the relative stereochemistry was tentatively assigned by NOESY analysis (Scheme 3.9). Using this assignment, the major tricyclic product **268** corresponds to the acyclic *syn/anti* diastereoisomer, in accordance with the other pyrrolidinone analogues.



Scheme 3.9: Tandem reaction using cyclic imine **268**.

To fully explore the utility of the tandem reaction, the use of alternative nucleophiles in the 1,4-addition reaction was necessary. With the use of diethylzinc proving successful, alternative dialkylzinc reagents were attempted. The reaction was successfully carried out using dimethylzinc to afford **270** in an excellent 64% yield (Scheme 3.10).



141 227 270

Scheme 3.10: Dimethylzinc addition to form pyrrolidinone **270**.

The reaction was also attempted using diphenylzinc. The reactivity of diphenylzinc is known to be lower than other dialkylzinc reagents,[103] therefore, two equivalents (previously 1.1) were used and the 1,4-addition reaction was left for three days before imine and TFA were added. Unfortunately, the crude reaction mixture showed only a complex mixture of degradation products, as well as the recovered imine **223**.

The tandem reaction was also attempted using PMP protected 3-indole imine. Unfortunately, the crude reaction mixture only contained the corresponding 1,4-addition product and recovered imine. It was later postulated that *N*-protection of the indole nitrogen, might prevent protonation with TFA during the reaction and therefore allow the nitro-Mannich to proceed. This strategy could allow for the reaction to be carried out using a range of nitrogen containing heterocycles in future studies.

3.4 Confirmation of Relative Stereochemistry

As described previously, the desired pyrrolidinones were formed as a single diastereoisomer, usually isolated as a crystalline solid. This allowed crystallographic analysis of selected structures to be conducted, to determine the relative stereochemistry across the three new stereocentres. Crystal structures of 4-trifluoromethyl- (**249**) and 2-bromo-4-fluoro (**256**) analogues were obtained, showing the same relative stereochemistry in both cases (Figure 3.1).

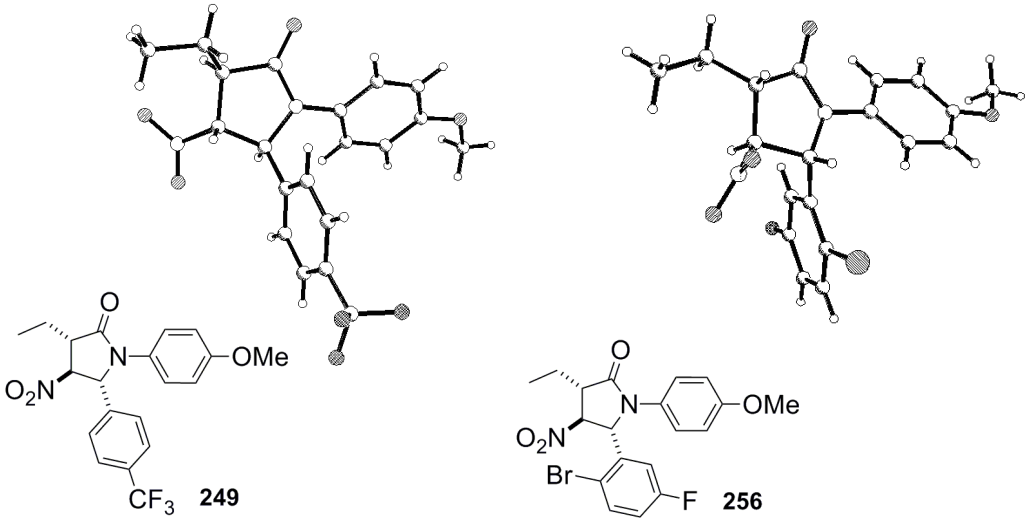


Figure 3.1: Confirmation of relative stereochemistry.

The relative stereochemistry of the remaining compounds were assigned by comparison of their ^{1}H NMR coupling constants. When considering coupling from H_A to H_B (J_1) (Figure 3.2) a range of 5.3-7.5 Hz was found for all analogues, with three exceptions. The pyrrolidinones bearing an ester-, cyclohexyl- and *ortho*-methoxy- substituent showed coupling of 4.3, 4.5 and 4.7 Hz respectively, which are marginally outside the range quoted. Coupling between H_B and H_C (J_2) fell within a range of 4.2-5.9 Hz, again with the ester analogue as an exception (3.4 Hz). As no other diastereoisomers of the pyrrolidinone product have been isolated, comparisons between coupling constants remains difficult. However, from the data collected it is fair to assume that the relative stereochemistry found in the X-ray crystallographic data (Figure 3.1) is also present in the other isolated analogues. A full table of coupling constants can be found in appendix 1 (see section 6.0).

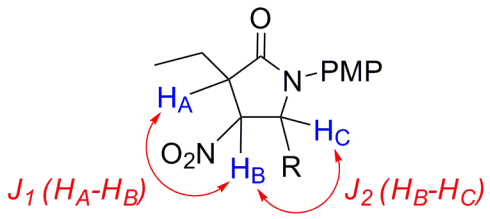


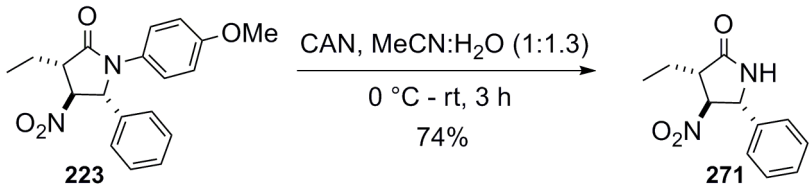
Figure 3.2: Comparison of ^{1}H NMR coupling constants.

3.5 Further Functionalisation

With a small library of pyrrolidinones successfully synthesised, the next challenge was to explore further functionalisation of the pyrrolidinone core. This would

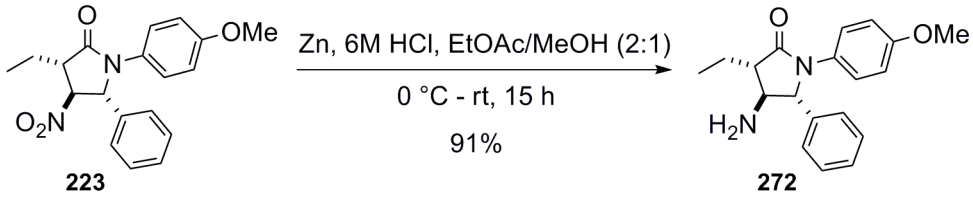
showcase the utility of the products and would enable the one pot route to highly functionalised pyrrolidinones to be utilised in synthesis.

The first task was to remove the PMP protecting group. This would provide the corresponding free amide and would enable further transformations to be conducted involving this nitrogen. An obvious choice for the removal of aromatic groups such as the PMP group was ceric ammonium nitrate (CAN).[104] Treatment of pyrrolidinone **223** with three equivalents of CAN in MeCN/H_2O over two hours gave a respectable 44% yield. Optimisation, by increasing the equivalents to four and the time to three hours gave an excellent 74% yield of the unprotected pyrrolidinone **271** (Scheme 3.11).



Scheme 3.11: Removal of PMP group.

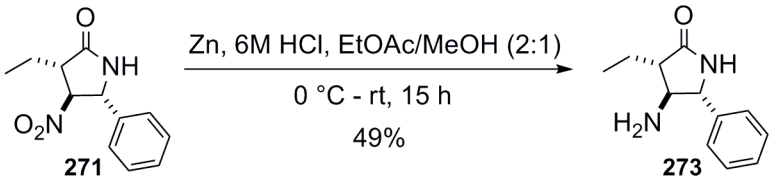
Reduction of the nitro group was also a requirement for the pyrrolidinone structure to be of future synthetic utility. This was performed using a Zn/HCl mixture (60:30 equivalents). These conditions worked well on this system, leading to a 91% yield of the primary amine **272** as a semi-solid (Scheme 3.12). The product **272** was found to be unstable to silica chromatography, which led to unidentifiable products. Fortunately, the crude reaction mixture was pure by ^{1}H NMR and would be suitable for use without purification.



Scheme 3.12: Reduction of nitro group.

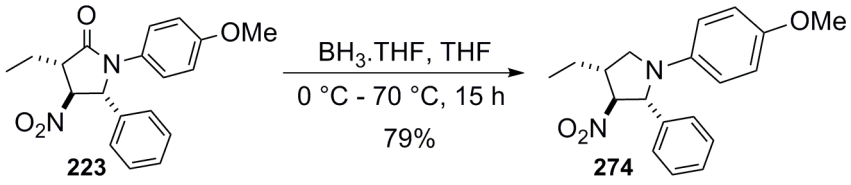
With both PMP removal and nitro reduction carried out successfully, attempts to isolate the unprotected diamine **273** were initiated. This would demonstrate the utility of the tandem nitro-Mannich process as a synthetically useful method for the formation of 1,2- or vicinal diamines. First attempts were performed by reduction of the nitro group to afford **272**, followed by deprotection with CAN. Unfortunately, the

material appeared to degrade under the oxidising conditions, therefore the reactions were carried out in the reverse order, preventing oxidative side reactions. Deprotection followed by reduction of the nitro group using the Zn/HCl conditions afforded **273** in 49% yield (Scheme 3.13). Although reduction proceeded smoothly to give a clean crude reaction mixture, the material was particularly unstable at room temperature and was also unstable to column chromatography. For this reason, **273** would require use immediately after the reaction, if used in synthesis.



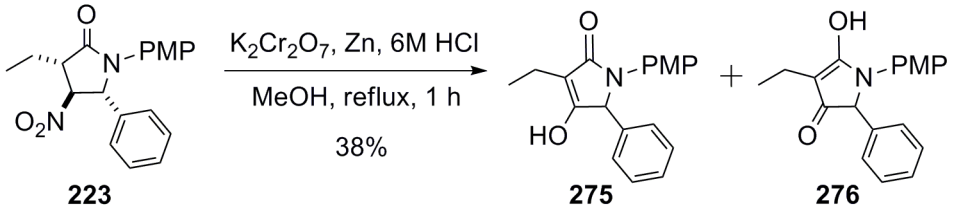
Scheme 3.13: Synthesis of unprotected vicinal diamine.

Use of the pyrrolidinone structure as a precursor to other heterocyclic structures was also important. With this in mind, reduction of the carbonyl group was investigated to furnish either the corresponding pyrroldinol, or pyrrolidine structures. Pyrrolidinone **223** was initially treated with Superhydride^{TM} (1.2 equivalents) at –78 °C however no change was observed (TLC analysis). The reaction was gradually warmed and eventually heated at reflux, however this resulted in degradation of the starting material. The reaction was also attempted with DIBAL, however only starting material was recovered after the addition of 10 equivalents and leaving for 15 hours at room temperature. Due to the observed stability of the pyrrolidinone, a more reactive hydride source was used. Reduction with BH_3.THF was carried out using 15 equivalents in THF at reflux for 15 hours. This successfully afforded the pyrrolidine **274** in a moderate yield, however some reduction of the nitro group was also observed. Reducing the number of equivalents to 3.5 under the same conditions, gave the desired pyrrolidine **274** in excellent 79% yield. Unfortunately, none of the corresponding hemi-aminal was seen in either of the BH_3.THF reactions (Scheme 3.14).



Scheme 3.14: Synthesis of pyrrolidine.

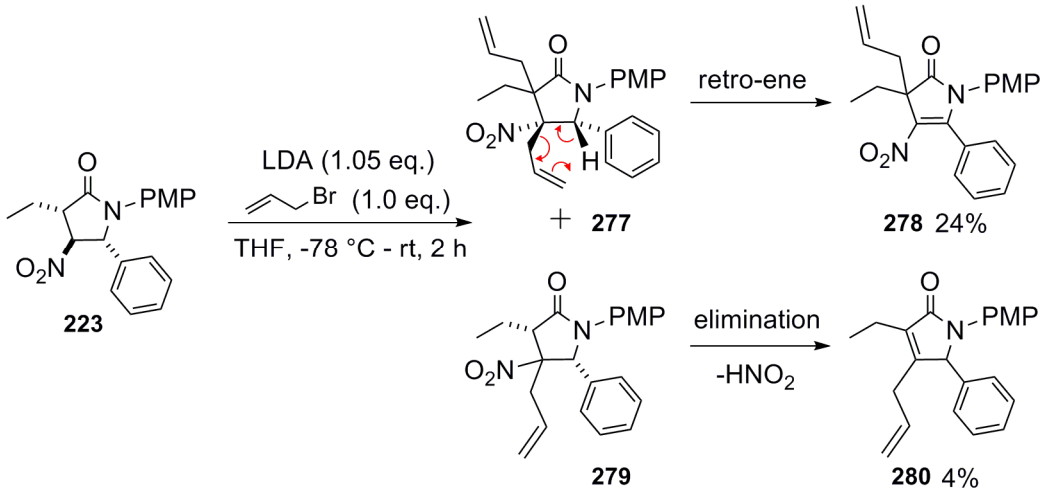
Further transformations involving the nitro group functionality would also be necessary for the pyrrolidinone to be a suitable building block in synthesis. Use of the Nef reaction, to yield the corresponding dicarbonyl compound would provide a useful method to allow further functional group interconversions at this position. Treatment of pyrrolidinone **223** with a 20% solution of $TiCl_3$ in 2M HCl,[105] was performed using an ammonium acetate buffer. Unfortunately, after three days at room temperature no reaction was observed and repeating the reaction without the buffer solution gave the same result. An alternative method was therefore attempted using chromium(II) dichloride produced *in situ* from reaction of potassium dichromate with 6M HCl and zinc dust.[106] Treatment of pyrrolidinone **223** with excess chromium dichloride in refluxing methanol gave the pyrrolones **275** and **276** as an inseparable 1:1 mixture of tautomers in 38% yield (Scheme 3.15). The remainder of the crude reaction mixture contained unreacted starting material and unidentified degradation products. Unfortunately, prolonging the reaction time did not drive the reaction to completion or provide any improvement in the yield.



Scheme 3.15: Synthesis of pyrrolones **275** and **276**.

In addition to the Nef reaction, functionalisation *via* deprotonation α to the nitro group would create highly functionalised molecules incorporating a quaternary centre. To this end, pyrrolidinone **223** was treated with LDA followed by the addition of allyl bromide. Unfortunately none of the desired product was seen however two additional compounds **278** and **280** were isolated in 24% and 4% yield respectively (Scheme 3.16). The major product **278** involves alkylation α to the nitro centre and α to the carbonyl to afford intermediate **277**. This then appears to

undergo a retro-ene reaction to give the observed product **278**. In contrast, isolation of **280** indicates that a small amount of the reaction is proceeding as desired to afford intermediate **279**, however this undergoes elimination of nitrous acid under the reaction conditions to give the observed product **280** (Scheme 3.16). Although this reaction is low yielding, it provides promising evidence that with optimisation of the reaction conditions, functionalisation α to the carbonyl as well as α to the nitro group could be performed.



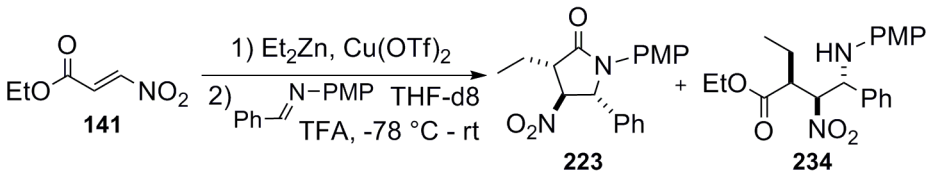
Scheme 3.16: Reaction of pyrrolidinone with allyl bromide.

3.6 Origins of Diastereoselectivity

With the scope of the three-component reaction fully explored, the reaction mechanism and in turn, the origins of the remarkable diastereoselectivity observed in this reaction, were examined. Many reports on the nitro-Mannich reaction, have predominately observed the *anti* diastereoisomer of the β-nitroamine as the major product.[46] In addition, studies towards a tandem 1,4-addition/nitro-Mannich reaction within the Anderson group, isolated the acyclic *syn/anti* β-nitroamine as the major product in the majority of cases, with some examples where the *syn/syn* diastereoisomer has predominated (see section 1.3).[100] When considering the 1,4-addition/nitro-Mannich/lactamisation reaction described herein, only one diastereoisomer of the pyrrolidinone was isolated (with the exception of tricyclic pyrrolidinone **269**, Scheme 3.9). Therefore it was necessary to further investigate the origins of diastereoselectivity in this three-step process.

Previous studies had found that if the reaction was quenched after just five minutes at room temperature, pyrrolidinone **223** was isolated in 16% yield along with 37% of a

mixture of other isomers, of which the acyclic *syn/anti* β-nitroamine diastereoisomer **234** was the major component.[100] To complement this study, the reaction was carried out using deuterated THF as the solvent. A sample of the reaction mixture was taken immediately after the addition of imine **227** and TFA. Analysis by ^{1}H NMR indicated the formation of an acyclic β-nitroamine as the major component, along with traces of other β-nitroamine diastereoisomers and a small proportion of the single pyrrolidinone product **223**. The major acyclic β-nitroamine is assumed to be the *syn/anti* diastereoisomer **234** (as isolated previously).[100] Although this assignment is based on circumstantial evidence, previous work within the Anderson group has also found that when the 1,4-addition/nitro-Mannich reactions were carried out in THF (and hence homogeneous) the *syn*/*anti* diastereoisomers have been unequivocally assigned as the major product. Further ^{1}H NMR analyses were then carried out at various time intervals, which indicated a gradual decrease of all β-nitroamine signals and in turn an increase in the single pyrrolidinone **223**. No other pyrrolidinone peaks were seen for the duration of this experiment (Table 3.5).



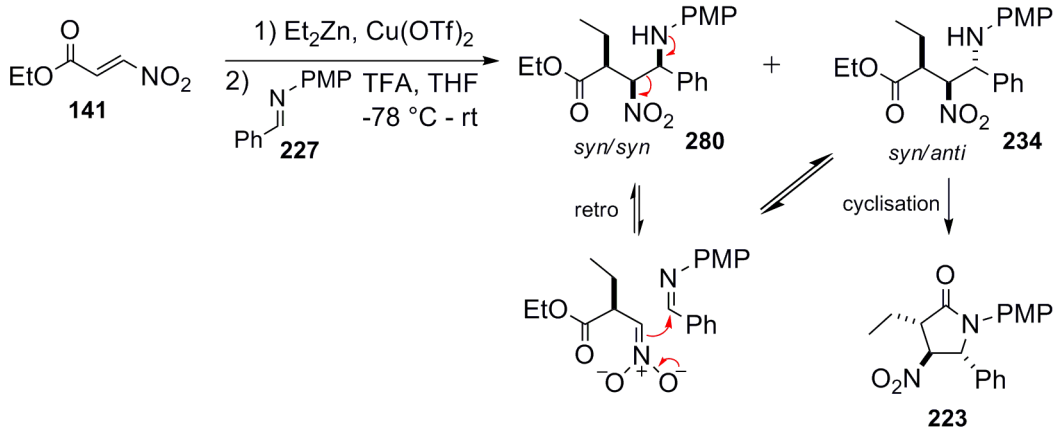
Entry	Time (min)	Ratio (223:234)
1	5	0.8:1
2	20	2:1
3	35	3.3:1
4	50	6.2:1
5	65	6.7:1
6	80	11.2:1

Ratio by ^{1}H NMR after warming from –78 °C to rt.

Table 3.5: ^{1}H NMR studies in deuterated THF.

This evidence suggests that under the reaction conditions, a mixture of β-nitroamine diastereoisomers are formed with the majority residing in the *syn/anti* conformation. Using, pyrrolidinone **223** as a model, it is known that the isolated pyrrolidinone **223**

corresponds to cyclisation of the *syn/anti* β-nitroamine **234**. Therefore due to the observation that only one pyrrolidinone is seen, it is postulated that cyclisation to form the pyrrolidinone **223** is more favourable for the *syn/anti* diastereoisomer **234**, than for the other possible diastereoisomers. As *syn/anti* **234** is consumed by cyclisation, it is suggested that the traces of other β-nitroamine diastereoisomers are gradually converted into the *syn/anti* product **234**, which can then undergo lactamisation to form the cyclic pyrrolidinone **223**. This conversion of diastereoisomers is thought to occur *via* a retro nitro-Mannich reaction (Scheme 3.17).



Scheme 3.17: Proposed mechanistic pathway to pyrrolidinones.

To consider the proposal that only the *syn/anti* β-nitroamine **234** favourably undergoes lactamisation, transition states for cyclisation of the possible diastereoisomers were considered. If the *syn*/*anti* diastereoisomer is able to cyclise faster under the reaction conditions, it is assumed that the activation energy for the pathway leading to this lactamisation must be lower than that for the other diastereoisomers. The two major diastereoisomers **234** and **281** (isolated in previous 1,4-addition/nitro-Mannich studies)[36] were considered. In accordance with this proposal, transition state **282** leading to the observed product **223** has all its substituents in *pseudo*-equatorial positions and thus represents an energy minima. In contrast when considering the *syn/syn* case, the transition state **283** leading to pyrrolidinone **284** would have one substituent in the axial position. Despite this, transition state **283** demonstrates that this pathway would not suffer from significant diaxial interactions and it is difficult to rationalise how this transition state could be of prohibitively higher energy. Although it is proposed that cyclisation occurs *via* the

lowest energy pathway, (*via* transition state **282**), the difference in energy between this and the pathway for the other transition states could be minimal (Figure 3.3).

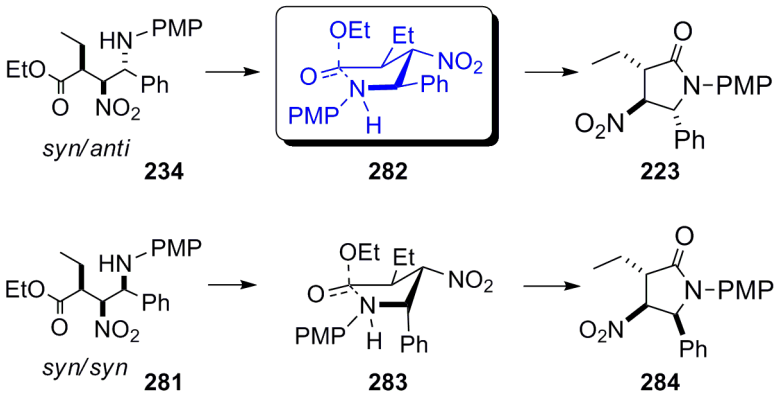
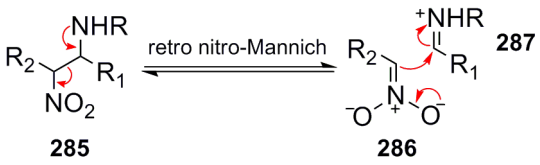


Figure 3.3: Conformational analysis of pyrrolidinone transition states.

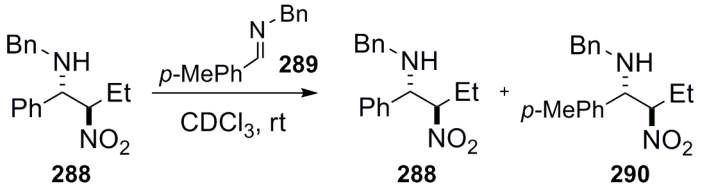
To analyse the origin of conversion of the remaining β-nitroamine diastereoisomers into *syn/anti* product **234**, further ^{1}H NMR studies were conducted. It is known that β-nitroamines **285** undergo retro nitro-Mannich reaction in solution at room temperature, to afford the corresponding nitronate **286** and recovered imine **287**. Therefore the retro nitro-Mannich explanation for degradation in diastereoselectivity is preferred over an epimerisation mechanism (Scheme 3.18).[107]



Scheme 3.18: Retro nitro-Mannich reaction.

To investigate this hypothesis, nitroamine **288** was synthesised from nitropropane and benzyl-protected phenyl imine, to afford a 10:1 mixture of the *anti:syn* diastereoisomers upon isolation. The isolated material was divided into two portions and dissolved in a small amount of $CDCl_3$. To one half was added 1.0 equivalent of benzyl protected 4-tolyl imine **289**, the other portion was used as a control experiment. Each sample was analysed by ^{1}H NMR at time intervals over a period of one week (Table 3.5). The results show a gradual deterioration in the diastereoselectivity, finishing with an *anti:syn* ratio of 1:2 in both the mixture and the control experiment. Analysis of the mixture also showed a gradual increase in the tolyl analogue **290** and respective decrease in the phenyl analogue **288** to an equilibrium value of 1:1. The observed changes in diastereoselectivity and formation

of the new β-nitroamine **290** clearly indicate the presence of a retro nitro-Mannich process under these conditions.



Entry	Time (h)	Control (288) (*anti:syn*)	Mixture (288) (*anti:syn*)	Mixture (290) (*anti:syn*)
1	0	10:1	10:1 (100%)	-
2	6	7.5:1	6.7:1 (93%)	>20:1 (7%)
3	20	4:1	3:1 (77%)	2:1 (23%)
4	30	3:1	2.1:1 (71%)	1.6:1 (29%)
5	48	2:1	1.2:1 (60%)	1.1:1 (40%)
6	72	1.3:1	1:1.5 (56%)	1:1.2 (44%)
7	144	1:1.8	1:2.7 (49%)	1:2 (50%)

Table 3.5: Retro nitro-Mannich studies.

With a proposed mechanistic pathway for the formation of the observed pyrrolidinone explored, it was important to consider the factors controlling the formation of the *syn/anti* β-nitroamine diasteroisomer **234** as the major intermediate in the three step reaction.

Control of diastereoselectivity for the initial conjugate addition intermediate will be dictated by the energetics of the electrophilic addition adjacent to an α-stereocentre. Houk *et al.* proposed a model which examines the effect of an α-stereocentre on electrophilic reactions at alkenes.[108] This model suggests that for this type of electrophilic reaction, the most electropositive substituent (in this case the ethyl group) should be arranged *anti* to the newly forming bond (Figure 3.4). This will maximise electron donation from the C-ethyl σ orbital to the developing C-electrophile bond (LUMO), hence having a stabilsing effect on the transition state for the reaction (Figure 3.4).

When considering the remaining two substituents on the α-centre, Houk proposed that if the smallest substituent on the α-centre (in this case the hydrogen) is oriented at the inside position (confirmation **291**), this would minimise 1,3-allylic strain between this small substituent (hydrogen) and substituents on the double bond (in this case the oxygen of the nitronate). It is also postulated that positioning the electron withdrawing group (in this case the ester) in the outside position, would minimise the dipole moment present in the corresponding transiton state. Taking both of these factors into consideration it is postulated that **291** would be the preferred conformation over **292** in this case. (Figure 3.4).

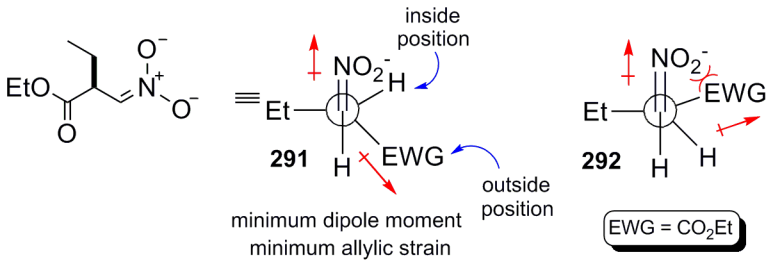


Figure 3.4: Configuration of α-centre substituents.

In addition to the substituents present on the α-centre, it is also necessary to consider the trajectory of the electrophile. Houk suggested that for a symmetrical alkene, the angle of attack would be 90° or less (Figure 3.5). However, placement of a donor substituent at one alkene terminus will cause donation of electron density into the anti-bonding π orbital, hence distorting the HOMO of the reaction. The attack angle will therefore increase to maximise overlap of the electrophile LUMO with the alkene (nitronate in this case) orbital with the largest coefficient (Figure 3.5).

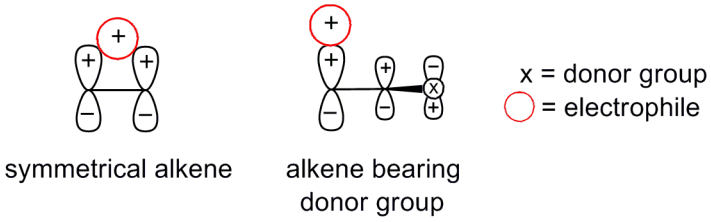


Figure 3.5: Orbital overlap with unsymmetrical alkenes.

This information indicates that in this case, the trajectory of the electrophile will be >90° and therefore some steric interactions between the electrophile and the ester (EWG) on the α-centre could occur (Figure 3.6). Despite this information, when considering the factors described above, it is postulated that conformation **293** would be the most favourable, minimising both the dipole moment and allylic strain in the

transition state. Analysis of **293** demonstrates that this correctly predicts the observed *syn* relationship between the ethyl and nitro stereocentres in the pyrrolidinone product (Figure 3.6).

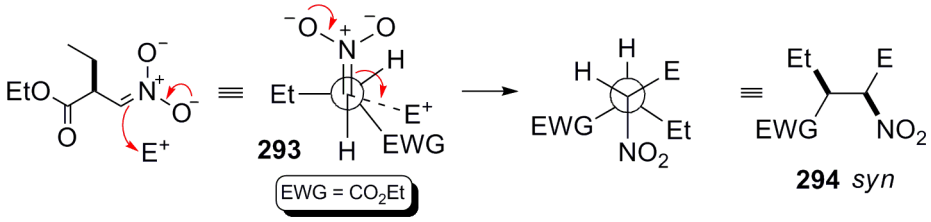


Figure 3.6: Favourable Newman projection and analysis of relative stereochemistry.

The relative stereochemistry between the two stereocentres formed in the nitro-Mannich reaction must also be considered. Previous studies have assumed a closed Zimmerman-Traxler like cyclic transition state between the nitronate and imine.[4] In this type of system, the imine prefers to adopt an *E*-geometry and therefore the substituent (R_1) will adopt a *psuedo*-axial position in the transition state (Figure 3.7). The lowest energy conformation will therefore place the remaining substituent (the nitronate side chain, R) in a *pseudo*-equatorial position, to avoid destabilising 1,3-diaxial interactions, leading to transition state **296**. If this side chain was in an axial position, as in transition state **295**, considerable 1,3,-diaxial strain would occur between the R group and the nitrogen protecting group (PMP). It is therefore suggested that the reaction proceeds *via* the more favourable transition state **296**. This conformation corresponds to the *anti* configuration across the two stereocentres, which is observed in the proposed *syn/anti* β-nitroamine intermediate and the pyrrolidinone product (Figure 3.7).

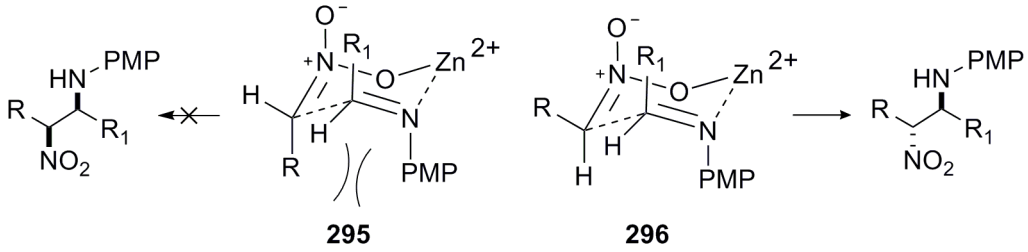
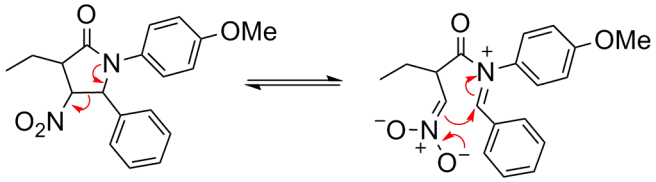


Figure 3.7: Zimmerman-Traxler transition state.

Although a good case has been made for the reaction mechanism and origin of diastereoselectivity, other factors must be considered. It is possible that the conversion of the other β-nitroamines formed in the reaction, into the *syn*/*anti* β-nitroamine could proceed *via* epimerisation rather than the proposed retro nitro-

Mannich reaction. However, it is postulated that this is less likely due to the non-basic nature of the reaction conditions.[109] In addition, previous studies on β-nitroamines using a suitable base to induce epimerisation, have seen significantly less deterioration in diastereoselectivity than was seen in the retro nitro-Mannich studies described above.[107] Another possibility is that more than one diastereoisomer of the pyrrolidinone are formed under the reaction conditions, which are converted to the observed product *via* an intramolecular retro nitro-Mannich mechanism (Scheme 3.19). This is also unlikely, as ^{1}H NMR analysis has shown no sign of other pyrrolidinone diastereoisomers. In addition, retro-addition is less likely as the pyrrolidinone system is protected as the cyclic lactam, reducing the availability of the nitrogen lone pair. Previous work within the Anderson group has shown that in the acyclic β-nitroamine case, when the nitrogen is protected with a trifuoroacetate group, the retro nitro-Mannich reaction is rarely seen.[100]



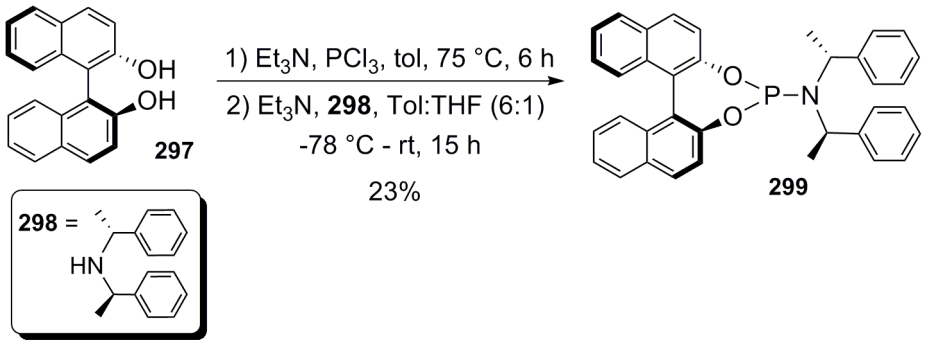
Scheme 3.19: Intramolecular retro nitro-Mannich pathway.

3.7 Asymmetric Methodology

To fully demonstrate the utility of the 'one pot' process, development of an asymmetric variant of the reaction was required. The asymmetric 1,4-addition of carbon nucleophiles to nitroalkenes is known and a number of reports in the literature have focussed specifically on nitroacrylates (see section 1.6). If the 1,4-addition step could be performed in an asymmetric fashion, it would be possible to obtain the pyrrolidinone products in enantiopure form. The aim was to use a ligand that would incorporate the current $Cu(OTf)_2$ catalyst system, used in the racemic series.

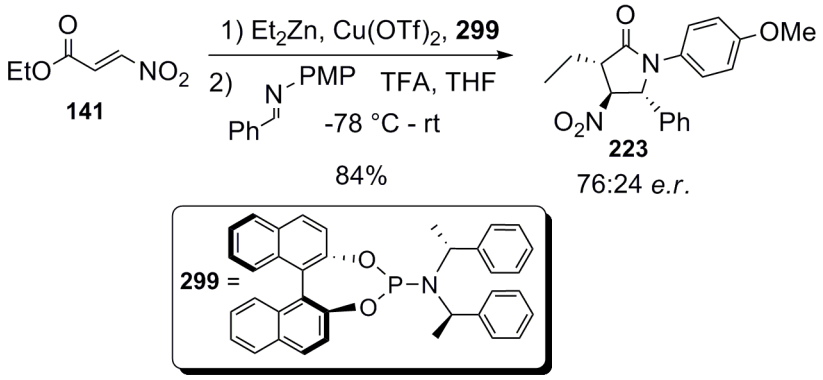
Feringa *et al.*,[110] have reported the asymmetric conjugate addition of dialkylzinc reagents to nitroalkenes in high yield and high enantioselectivity using a combination of a copper(II) catalyst with a variety of phosphoramidite ligands. Sewald *et al.*,[79] subsequently reported the same use of phosphoramidites specifically for nitroacrylates. It was therefore proposed that this methodology could be applied to the 1,4-addition/nitro-Mannich/lactamisation reaction. A suitable catalyst **299** was

synthesised according to literature procedures (Scheme 3.20).[111] Treatment of (+)-bis[(*R*)-1-phenylethyl]amine-hydrochloride with triethylamine gave the free amine **298**. Additional triethylamine and phosphorous trichloride were added and the reaction was heated at 75 °C for 6 hours. The reaction was then cooled and (*S*)-(-)-1,1'-bis(2-napthol) **297** was added to yield the desired phosphoramidite **299** in 23% yield, (lit.[111] 20%). The low isolated yield was similar to that reported in the literature which is attributed to the instability of the product when using silica chromatography (Scheme 3.20).



Scheme 3.20: Synthesis of phosphoramidite catalyst.

Phosphoramidite **299** was then used in the tandem reaction under the reaction conditions described in the literature.[111] This gave an excellent yield of the pyrrolidinone (84%) and HPLC analysis by comparison with a racemic sample, showed 76:24 *e.r.* (52% *e.e.*) (Scheme 3.21).



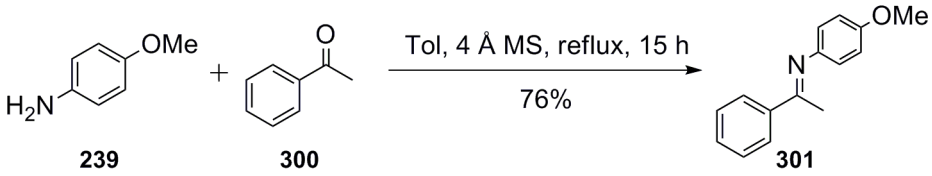
Scheme 3.21: Enantioselective formation of the pyrrolidinone.

When using the same catalyst, Sewald obtained yields between 70-94% for the corresponding 1,4-addition product, with an *e.e.* of 77%. This was subsequently improved to 92% *e.e.* when using a similar ligand with *o*-3,3'-methyl substituents present on the BINOL portion of the molecule. Due to time constraints no other

asymmetric ligands were screened at this time, however a number of similar ligands have been reported,[112] which could be suitable for developing this reaction enantioselectively. With this promising result it is hoped that the enantioselectivity could be improved with modifications to the phosphoramidite **299**, or use of alternative ligands.

3.8 Further Development

In an attempt to further develop the scope of the tandem reaction, use of a ketimine was investigated. This could allow generation of a quaternary centre and increase the functionality of the pyrrolidinone ring. A simple ketimine **301** derived from *p*-anisidine (**239**) and acetophenone (**300**) was synthesised to give the desired product **308** in 76% yield (Scheme 3.22).



239 **300** **301**

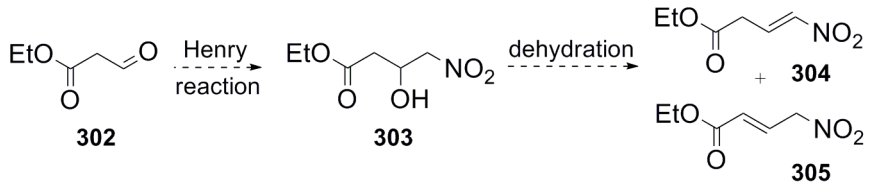
Scheme 3.22: Synthesis of ketimine **301**.

The tandem reaction was attempted under the standard conditions using the new ketimine **301**. Unfortunately after 15 hours at room temperature the crude reaction mixture showed only 1,4-addition product. In addition, performing the reaction in THF at reflux, (after the addition of ketimine and TFA), showed no traces of either nitro-Mannich or cyclisation product.

With the synthesis and scope of the pyrrolidinone structure successfully investigated, it was postulated that the methodology could be expanded to synthesise the corresponding six membered piperidinone. A synthesis of this type would be complimentary to methodology reported by Dixon *et al.* which utilises cyclic imines and γ-nitro esters in a nitro-Mannich/lactamisation cascade.[53]

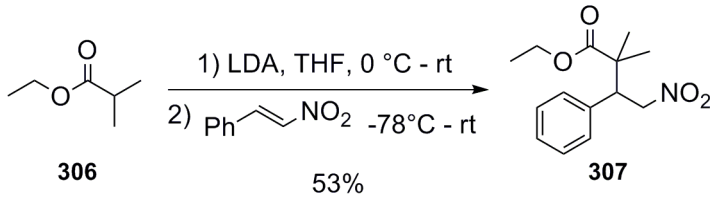
Employing the same principles used in the pyrrolidinone case would require the synthesis of the corresponding extended nitroacrylate **305**. However, a search of the literature provided no suitable routes to the desired nitroalkene **305** and it was postulated that control of the regioselectivity with respect to the new double bond,

would be difficult when using the previously used Henry/dehydration route (Scheme 3.23).



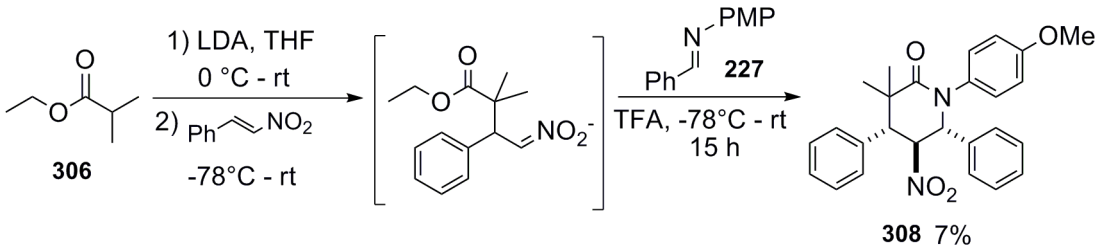
Scheme 3.23: Problematic route to the desired nitroalkene **305**.

Due to these problems, an alternative method was devised. Focus was turned to installing the ester functionality *via* the initial 1,4-addition reaction. Treatment of ethyl isobutyrate **306** (1.2 equivalents with respect to the nitroalkene) with LDA, followed by addition of nitrostyrene and warming to room temperature, afforded 1,4-addition product **307** in 53% yield (Scheme 3.24).



Scheme 3.24: 1,4-addition of ethyl isobutyrate.

With 1,4-addition proving successful, the one pot 1,4-addition/nitro-Mannich/lactamisation reaction was attempted. Treatment of ethyl isobutyrate with LDA was carried out as demonstrated previously, followed by the addition of nitrostyrene, PMP protected phenyl imine and TFA. The crude reaction mixture showed mainly 1,4-addition product, with traces of both acyclic β-nitroamine and pleasingly, a small amount of the desired six membered ring **308**. Purification by silica chromatography gave an isolated yield of 7%, with relative stereochemistry as suggested below (Scheme 3.25).



Scheme 3.25: Synthesis of piperidinone **308**.

It is suggested that control of diastereoselectivity in this reaction will again be dictated by the energetics of electrophilic addition adjacent to an α-stereocentre. When considering the principles described previously for diastereoselective electrophilic additions (see section 3.6), it is proposed that in this case the reaction is dictated by sterics, due the presence of a large bulky group (R) on the α-centre. It is proposed that the largest group (in this case R) (Figure 3.8) should be arranged *anti* to the newly forming bond. The remaining groups will be positioned so that the electrophile will encounter the least steric influence during the reaction. Therefore, the smallest substituent on the α-centre (in this case the hydrogen) would be oriented in the outside position and the phenyl group in the inside position. When considering these factors, analysis of Newman projection **309** indicates an *anti* relationship between the two newly formed stereocentres (**310**) (Figure 3.8).

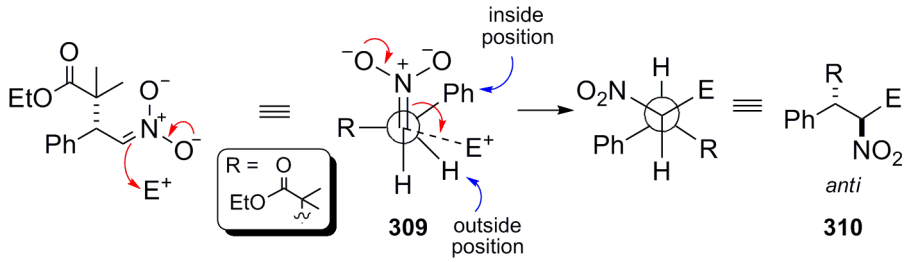


Figure 3.8: Proposed relative stereochemistry for piperidinone **308**.

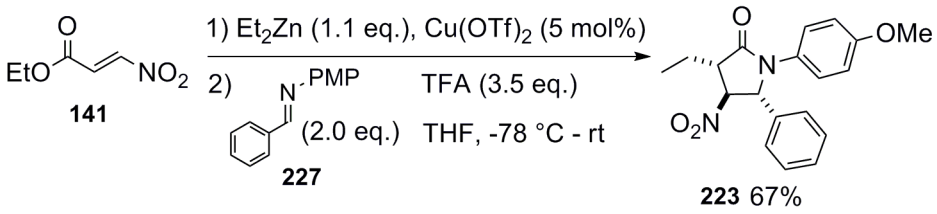
In turn, if the nitro-Mannich reaction is governed by a closed Zimmerman-Traxler transition state as described previously (see section 3.6) the relative stereochemistry formed in the nitro-Mannich reaction will also assume the *anti* configuration, as in the pyrrolidinone case. Although additional experiments would be necessary to further investigate the origin of this diastereoselectivity, the intermediate β-nitroamine formed in the reaction can therefore be tentatively assigned as the *anti/anti* diastereoisomer, which in turn corresponds to the suggested piperidinone product **308**. In addition, Dixon *et al.* reported a nitro-Mannich cascade for the synthesis of similar piperidinone derivatives, which demonstrated the same relative stereochemical configuration as suggested here.[53]

Although this reaction is low yielding, this example represents a promising result for future studies. Optimisation of the reaction conditions, as well as appropriate choice of nucleophile, nitroalkene and imine partners, could lead to a valuable tandem process for the synthesis of highly functionalised piperidinone structures.

4.0 Conclusions and Future Studies

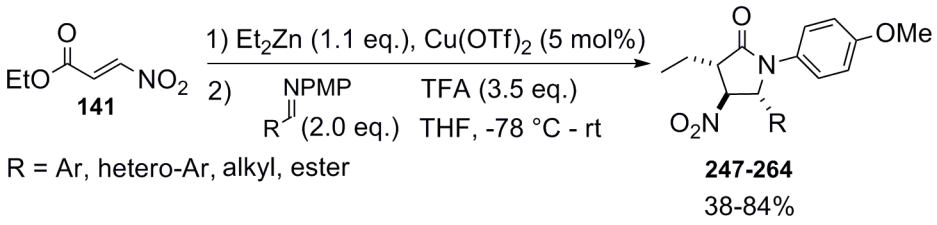
4.1 Conclusions

This chapter has described the successful development of a 1,4-addition/nitro-Mannich/lactamisation reaction for the stereoselective synthesis of pyrrolidinones. Initial work began with optimisation of the reaction conditions. This was carried out by treatment of nitroacrylate **141** with diethylzinc, in the presence of $Cu(OTf)_2$, followed by addition of the PMP-protected imine derived from benzaldehyde and TFA. Each reaction parameter was carefully optimised in turn to afford an excellent 67% overall yield of the pyrrolidinone **223** as a single diastereoisomer (Scheme 4.0).



Scheme 4.0: Optimised conditions for the pyrrolidinone reaction.

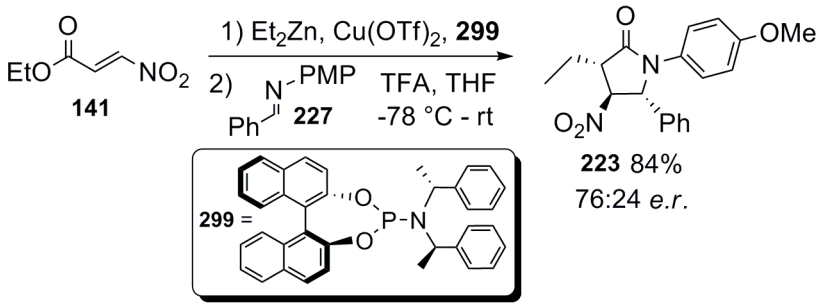
With optimsation completed, the scope of the reaction was explored by employing a variety of alkyl and aryl substituted imines. Aromatic substituents bearing both electron-donating and electron-withdrawing groups were examined, as well as heteroaromatic and a variety of alkyl substituted imines. This study afforded 18 analogues of the pyrrolidinone product, in 38-84% yield, each isolated as a single diastereoisomer (Scheme 4.1).



Scheme 4.1: Synthesis of pyrrolidinone analogues.

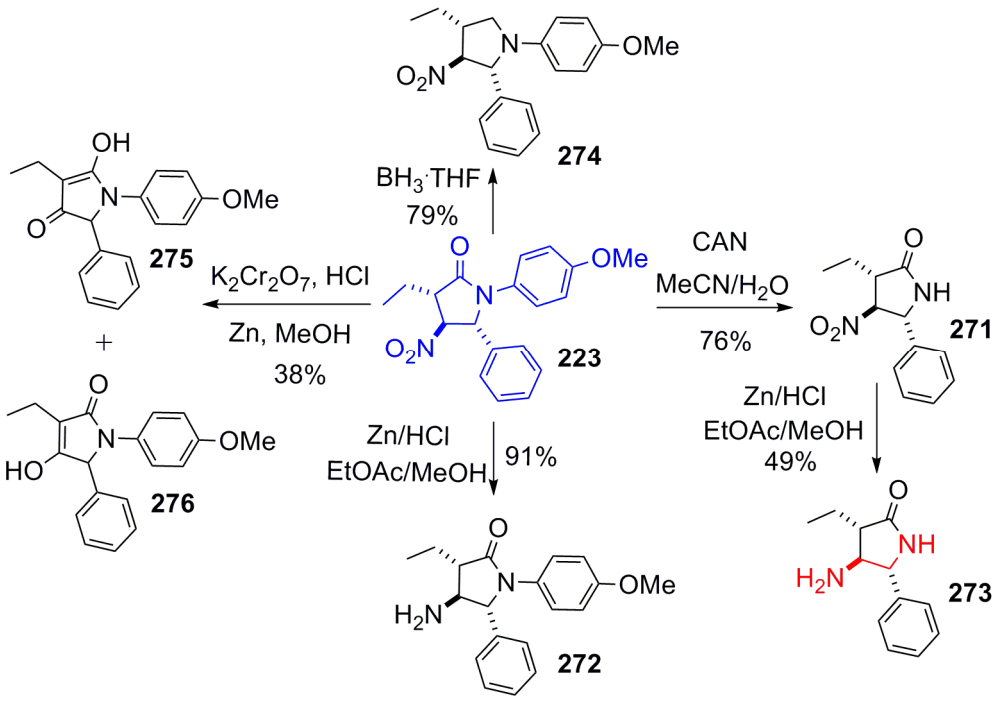
In addition to the use of PMP-protected imines, cyclic imine **268** derived from tetrahydroisoquinoline was also utilised, to yield the tricyclic pyrrolidinone **269** as a 5:1 mixture of diastereoisomers, in 60% yield. Alternative dialkylzinc reagents were also investigated, with dimethylzinc allowing successful formation of the corresponding pyrrolidinone **270** in 64% yield.

Development of an enantioselective variant of the reaction was then explored. The asymmetric conjugate addition of diorganozinc reagents to nitroacrylates had previously been reported in the literature (see section 1.6.3). This technology was therefore appied to the three-step reaction to allow formation of the pyrrolidinone in enantiopure form. Synthesis of Feringa's phosphoramidite ligand **299** was carried out and subsequently employed in the one pot reaction. Successful asymmetric induction was achieved, giving a moderate 52% *e.e.* (76:24 *d.r.*) and an excellent 84% yield for the three-step reaction (Scheme 4.2).[113]



Scheme 4.2: Enantioselective synthesis of pyrrolidinones.

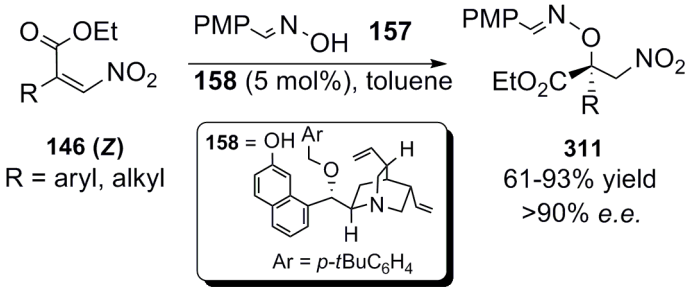
Finally, with the pyrrolidinone structure in hand, further functionalisation was explored. The first challenge was removal of the PMP protecting group, which was successfully achieved using CAN in MeCN/H_2O to afford **271** in 76% yield (Scheme 4.3). Reduction of the nitro group was also performed successfully using Zn/HCl, which allowed isolation of the important 1,2- or vicinal diamine motif **273** in 91% yield. Reduction of the carbonyl group using the BH_3.THF complex was performed in excellent 79% yield (**274**) and Nef reaction of the nitro group, affording the corresponding carbonyl **275** and **276**, was achieved in 38% yield (Scheme 4.3). These successful functional group interconversions indicate that the pyrrolidinone structure could be used as an important building block in synthesis.



Scheme 4.3: Further functionalisation of the pyrrolidinone structure.

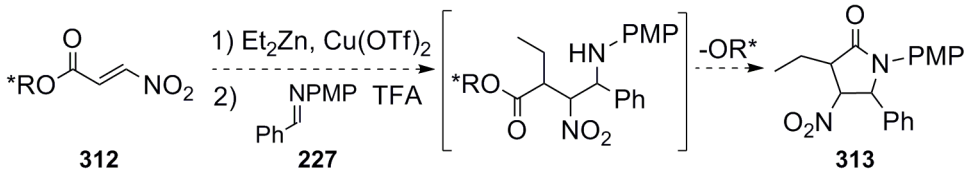
4.2 Future Studies

With the synthesis of a wide range of pyrrolidinone analogues proving highly successful, there are many opportunities for further study in this area. One such area would involve use of alternative nucleophiles. Although there are numerous reports on the synthesis and use of alternative diorganozinc reagents, few are commercially available and many involve laborious procedures to obtain pure reagents. Despite this, there are many examples exploring the conjugate addition to nitroacrylates using heteroatom nucleophiles (Scheme 4.4).[78] If the development of this reaction using alternative nucleophiles could be achieved, this would result in a large improvement in the scope of the reaction and the structures that could be synthesised *via* this route.



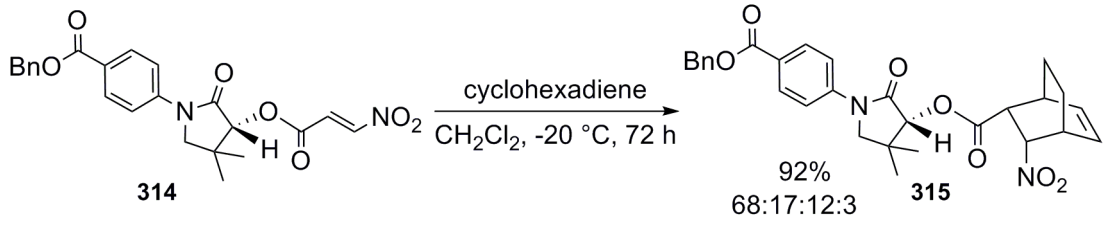
Scheme 4.4: Oxime addition to nitroacrylates **146**.

With the three-step reaction proving highly diastereoselective, it would also be desirable to render the reaction asymmetric. With initial results proving successful using the phosphoramidite ligand **299**, small modifications to the ligand structure could improve the enantioselectivity and enable this methodology to be used in asymmetric synthesis. To develop this idea further, use of an appropriate nitroacrylate bearing a chiral substituent, could also enable the reaction to proceed enantioselectively. The conjugate addition/nitro-Mannich reaction could be carried out as described previously, followed by *in situ* lactamisation, allowing the chiral substituent to be removed under the reaction conditions (Scheme 4.5).



Scheme 4.5: Proposed use of a chiral nitroacrylate.

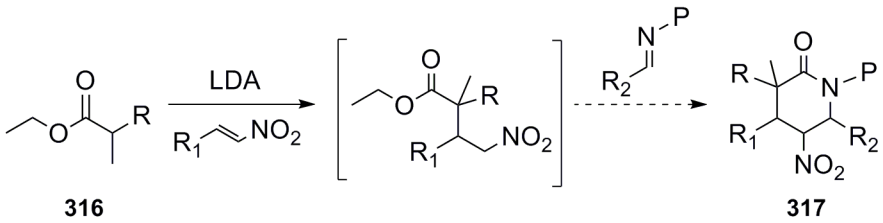
Reports in the literature have demonstrated that the 1,4-addition of chiral substrates to nitroalkenes can enable the reaction to be achieved enantioselectively (see section 1.6.1). In addition, the chiral nitroacrylate **314** has been used to induce selectivity in the cycloaddition reaction with cyclohexadiene, to afford the corresponding nitro adduct **315** as a mixture of *endo* and *exo* isomers in a 68:17:12:3 ratio (Scheme 4.6).[114] Although this demonstrates only modest selectivity, this example provides promising evidence that nitroacrylates of this type could be utilised to induce enantio-induction and hence afford the pyrrolidinones in enantiopure form.



Scheme 4.6: Cycloaddition using chiral nitroacrylate **314**.

With the pyrrolidinone synthesis proving highly successful, it is proposed that a similar process could be employed for the corresponding six membered ring. Preliminary experiments (see section 3.8), have indicated that with optimisation of the reaction conditions, the desired products could be isolated in good yield and

diastereoselectivity, which could in turn led to a large array of analogous six membered ring structures (Scheme 4.7).



316 **317**

Scheme 4.7: Possible scope of the six membered ring analogues.

5.0 Experimental

5.1 General Experimental Details

For all non-aqueous chemistry, glassware was flame dried and reactions were carried out under an inert (N_2) atmosphere. For all air sensitive chemistry, Schlenk glassware was flame dried under vacuum and reactions were carried out under a flow of argon. Cooling to 0 °C was affected using an ice-water bath. Cryogenic conditions (-78 °C) were achieved using a solid carbon dioxide-acetone bath. Degassing of solutions was carried out by freezing the solution using liquid N_2, subjecting the flask to vacuum, followed by slowly warming to room temperature. This was repeated three times. For the purpose of thin layer chromatography, Polygram® SilG/UV_{254} 0.25 mm silica gel plates were used. Visualisation was achieved using ultraviolet light, (254nm) and/or anisaldehyde or $KMnO_4$ solutions as appropriate. Removal of solvents (*in vacuo*) was achieved using a water aspirator and Büchi rotary evaporators. Flash column chromatography was performed using Geduran® silica gel 60, 40-63 μm.

5.2 Analytical Instruments and Characterisation

All ^1H, ^{19}F and ^{13}C NMR data were recorded using Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz, Bruker AVANCE III 600 MHz. Data was manipulated directly using Bruker XwinNMR (version 2.6) or Topspin (version 2.1). Samples were made as dilute solutions of $CDCl_3$ unless otherwise stated. All chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. δ = 7.27 for ^1H NMR and δ = 77.2 for ^{13}C NMR in $CDCl_3$. Multiplicities for ^1H coupled signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Coupling constants (*J*) are reported in Hertz. ^{13}C multiplicities were assigned using a DEPT sequence. Where appropriate, HMQC, COSY, HMBC, NOESY experiments were carried out to aid assignment.

Mass spectra were acquired on Thermo Finnigan Mat900xp **(**EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data was collected using Perkin-Elmer 1600 FTIR machine as a thin film unless otherwise stated. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Melting points are uncorrected and were recorded on a Stuart Scientific SMP3 system. Optical rotations were obtained using a Jasco DIP370 digital polarimeter and

are reported in deg cm^2 g^{-1}. X-ray crystallography was carried out using a Bruker SMART APEX CCD diffractometer.

5.3 Purification of Solvents and Reagents

Commercial solvents and reagents were used as supplied or purified in accordance with standard procedures.[115]

Acetophenone was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

Benzaldehyde was distilled from calcium hydride powder under an atmosphere of nitrogen, and stored in a darkened fridge.

Copper(II) triflate was stored in an inert atmosphere box and used immediately after being weighed out.

Dichloromethane (CH_2Cl_2) was obtained from a solvent tower, where degassed dichloromethane was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Diethyl ether (Et_2O) was obtained from a solvent tower, where degassed diethyl ether was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Diisopropylethylamine (DIPEA) was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

Tetrahydrofuran (THF) was obtained from a solvent tower, where degassed tetrahydrofuran was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Triethylamine (Et_3N) was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

Toluene was obtained from a solvent tower, where degassed toluene was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

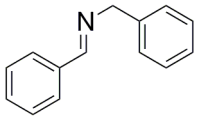
All solutions of organolithium reagents were standardised with diphenyl acetic acid.

Activation of 4 Å molecular sieves was achieved by heating under high vacuum.

5.4 Experimental Procedures

5.4.1 Preparation of Imines and Nitroalkenes

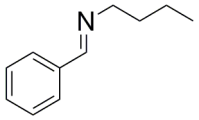
Benzyl-[1-phenylmeth-(*E*)-ylidene]-amine (318)[116]



318

To a solution of benzylamine (1.31 mL, 10.4 mmol, 1.1 equiv.) in CH_2Cl_2 (47 mL) under N_2 was added 4 Å MS (10.4 g, 1.0 g per mmol) and the mixture stirred at rt for 5 min before benzaldehyde (1.00 g, 9.43 mmol) was added. The mixture was stirred for a further 15 h before being filtered through celite® and washed with CH_2Cl_2 (2 x 20 mL). The filtrate was concentrated *in vacuo* to give **318** (1.31 g, 71%, lit.[116] 67%) as a yellow oil, which was used without further purification; ^{1}H NMR (400 MHz) δ 4.88 (2H, s, C*H*$_2$Ph), 7.27-7.35 (1H, m, Ar*H*), 7.41 (4H, d, *J* = 4.4, Ar*H*), 7.45-7.50 (3H, m, Ar*H*), 7.83 (1H, d, *J* = 4.8, Ar*H*), 7.86 (1H, d, *J* = 2.0, Ar*H*), 8.44 (1H, s, C*H*N). Data in agreement with that reported.[116]

Butyl-[1-phenylmeth-(*E*)-ylidene]-amine (319)[117]



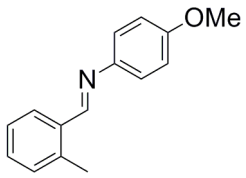
319

To a solution of *n*-butylamine (1.06 mL, 10.4 mmol, 1.1 equiv.) in CH_2Cl_2 (47 mL) under N_2, was added Al_2O_3 (10.4 g, 1.0 g per mmol) and the mixture stirred at rt for 5 min before benzaldehyde (1.00 g, 9.43 mmol) was added. The mixture was stirred for a further 15 h before being filtered through celite® and washed with CH_2Cl_2 (2 x 20 mL). The filtrate was concentrated *in vacuo* to give **319** (1.21 g, 80%, lit.[117] 34%) as a yellow oil, which was used without further purification; ^{1}H NMR (500 MHz) δ 0.96 (3H, t, *J* = 7.3, CH_2CH_3), 1.36-1.44 (2H, m, CH_2CH_3), 1.66-1.72 (2H, m, NCH_2CH_2), 3.62 (2H, td, *J* = 7.0, 1.5, NCH_2), 7.39-7.41 (3H, m, Ar*H*), 7.72-7.74 (2H, m, Ar*H*), 8.24 (1H, s, C*H*N). Data in agreement with that reported.[117]

General Procedure A: Synthesis of PMP Imines

To a solution of 4-anisidine (1.10 mmol) in CH_2Cl_2 (5 mL per mmol) under N_2 was added 4 Å MS (1.0 g per mmol) and the mixture stirred at rt for 5 min. Aldehyde (1.00 mmol) was then added and the mixture stirred for a further 15 h before being filtered through celite® and washed with CH_2Cl_2 (5 mL per mmol). The filtrate was concentrated *in vacuo* to give crude imine.

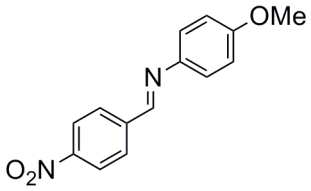
(4-Methoxyphenyl)-[1-(2-tolyl)-meth-(*E*)-ylidene]-amine (240)[118]



240

Prepared by general procedure A: 4-Anisidine (1.00 g, 8.12 mmol) and 2-methyl-benzaldehyde (870 μL, 7.38 mmol) afforded crude imine **240**. Purification by recrystallisation (EtOAc/hexanes) gave **240** (1.83 g, 63%, lit.[118] yield not reported) as a yellow solid; mp. 45-47 °C (no lit. mp. reported); ^{1}H NMR (400 MHz) δ 2.60 (3H, s, ArC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 6.94-6.98 (2H, m, Ar*H*), 7.22-7.27 (3H, m, Ar*H*), 7.29-7.38 (2H, m, Ar*H*), 8.09 (1H, dd, *J* = 7.6, 1.6, Ar*H*), 8.79 (1H, s, C*H*N). Data in agreement with that reported.[118]

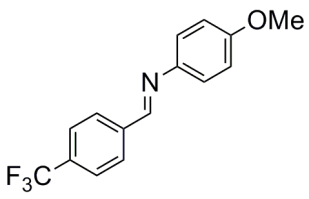
(4-Methoxyphenyl)-[1-(4-nitrophenyl)-meth-(*E*)-ylidene]-amine (241)[119]



241

Prepared by general procedure A: 4-Anisidine (1.00 g, 8.12 mmol) and 4-nitro-benzaldehyde (720 μL, 7.38 mmol) gave crude imine **241**. Purification by recrystallisation (EtOAc/hexanes) gave **241** (1.67 g, 88%, lit.[119] 94%) as an orange solid; mp. 118-120 °C (lit.[119] mp. 133-134 °C); ^{1}H NMR (400 MHz) δ 3.87 (3H, s, OC*H*$_3$), 6.96-7.00 (2H, m, Ar*H*), 7.28-7.35 (2H, m, Ar*H*), 8.06-8.09 (2H, m, Ar*H*), 8.32-8.35 (2H, m, Ar*H*), 8.60 (1H, s, C*H*N). Data in agreement with that reported.[119]

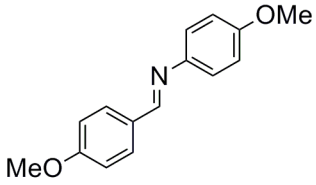
(4-Methoxyphenyl)-[1-(4-trifluoromethylphenyl)-meth-(*E*)-ylidene]-amine (242)[116]



242

Prepared by general procedure A: 4-Anisidine (1.00 g, 8.12 mmol) and 4-trifluoromethylbenzaldehyde (1.09 mL, 6.99 mmol) gave crude imine **242**. Purification by recrystallisation (EtOAc/hexanes) gave **242** (1.95 g, 88%, lit.[116] 81%) as a yellow solid; mp. 110-112 °C, (lit.[116] mp. 126-127 °C); ^{1}H NMR (500 MHz) δ 3.84 (3H, s, OC*H*$_3$), 6.95-6.96 (2H, m, Ar*H*), 7.26-7.29 (2H, m, Ar*H*), 7.71 (2H, d, *J* = 8.0, Ar*H*), 7.99 (2H, d, *J* = 8.0, Ar*H*), 8.53 (1H, s, C*H*N). Data in agreement with that reported.[116]

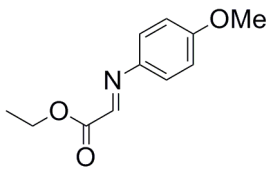
(4-Methoxyphenyl)-[1-(4-methoxyphenyl)-meth-(*E*)-ylidene]-amine (243)[119]



243

Prepared by general procedure A: 4-Anisidine (0.99 g, 8.10 mmol) and 4-methoxy-benzaldehyde (0.89 mL, 7.40 mmol) gave crude imine **243**. Purification by recrystallisation (EtOAc/hexanes) gave **243** (1.57 g, 88%, lit.[119] 93%) as a yellow solid; mp. 136-138 °C (lit.[119] mp. 144 °C); ^{1}H NMR (400 MHz) δ 3.84 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 6.95-7.01 (4H, m, Ar*H*), 7.20-7.27 (2H, m, Ar*H*), 7.83-7.86 (2H, m, Ar*H*), 8.42 (1H, s, C*H*N). Data in agreement with that reported.[119]

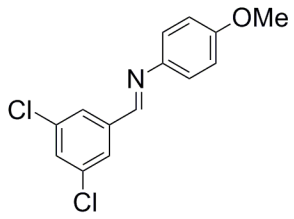
[(*E*)-4-Methoxyphenylimino]-acetic acid ethyl ester (244)[120]



244

To a solution of 4-anisidine (2.50 g, 20.3 mmol) and Na_2SO_4 (10.0 g) in toluene (20 mL) under N_2 at 0 °C was added ethyl glyoxylate (4.10 mL, of a 50% sol. in toluene, 20.3 mmol). The mixture was stirred at 0 °C for 1 h before being filtered and concentrated *in vacuo* to give **244** (4.12 g, 98%, lit.[120] 98%) as a bright yellow oil which was used without further purification; ^{1}H NMR (400 MHz) δ 1.40 (3H, t, *J* = 7.2, CH_2CH_3), 3.84 (3H, s, OCH_3), 4.41 (2H, q, *J* = 7.2, CH_2CH_3), 6.92-6.94 (2H, m, Ar*H*), 7.35-7.38 (2H, m, Ar*H*), 7.94 (1H, s, C*H*N). Data in agreement with that reported.[120]

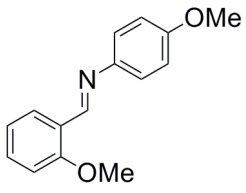
(4-Methoxyphenyl)-[1-(3,5-dichlorophenyl)-meth-(*E*)-ylidene]-amine (246)



246

Prepared by general procedure A: 4-Anisidine (770 mg, 6.29 mmol) and 3,5-dichloro-benzaldehyde (1.00 g, 5.71 mmol) gave crude imine **246**. Purification by recrystallisation (EtOAc/hexanes) gave **246** (1.66 g, 99%) as a bright yellow solid; mp. 64-66 °C; IR υ_{max} 3076 (CH), 3001 (CH), 2954 (CH), 2888 (CH), 2835 (CH), 1623 (C=N), 1583, 1561, 1505, 1248 (C-O), 1193 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.85 (3H, s, OCH_3), 6.94-6.98 (2H, m, Ar*H*), 7.24-7.28 (2H, m, Ar*H*), 7.44 (1H, t, *J* = 1.9, Ar*H*), 7.78 (2H, d, *J* = 1.9, Ar*H*), 8.39 (1H, s, C*H*N); ^{13}C NMR (150 MHz) δ 55.6 (OCH_3), 114.6 (2 x Ar), 122.6 (2 x Ar), 126.8 (2 x Ar), 130.7 (Ar), 135.6 (2 x Cq), 139.4 (Cq), 143.7 (Cq), 154.8 (N*C*H), 159.1 (Cq); *m/z* (CI$^+$) 280 (100%, MH$^+$), 244 (50%, MH$^+$-Cl); HRMS: found 280.0302, $C_{14}H_{12}NOCl_2$ requires 280.0296; Anal. Cald. For $C_{14}H_{11}NOCl_2$: C, 60.02, H, 3.96, N, 5.00. Found C, 60.03, H, 3.90, N, 4.94%.

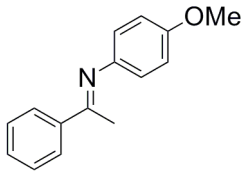
(4-Methoxyphenyl)-[1-(2-methoxyphenyl)-meth-(*E*)-ylidene]-amine (245)[121]



245

Prepared by general procedure A: 4-Anisidine (0.99 g, 8.10 mmol) and 2-methoxy-benzaldehyde (1.00 g, 7.34 mmol) gave imine **245** (1.79 g, 94%, lit.[121] yield not reported) as an orange solid, which was used without further purification; mp. 38-40 °C, (no lit. mp. reported); ^{1}H NMR (400 MHz) δ 3.86 (3H, s, OC*H*$_3$), 3.92 (3H, s, OC*H*$_3$), 6.93-6.98 (3H, m, Ar*H*), 7.04-7.08 (1H, m, Ar*H*), 7.25-7.29 (2H, m, Ar*H*), 7.45 (1H, ddd, *J* = 8.4, 7.4, 1.8, Ar*H*), 8.16 (1H, dd, *J* = 7.7, 1.8, Ar*H*), 8.96 (1H, s, C*H*N). Data in agreement with that reported.[121]

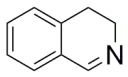
(4-Methoxyphenyl)-[1-phenyleth-(*E*)-ylidene]-amine (301)[122]



301

To a solution of 4-anisidine (1.00 g, 8.12 mmol) in toluene (50 mL) under N_2 was added 4 Å MS (8.0 g) and the mixture stirred at rt for 5 min before acetophenone (1.14 mL, 9.74 mmol, 1.2 equiv.) was added. The mixture was stirred at reflux for 15 h before being cooled to rt, filtered through celite® and washed with toluene (2 x 20 mL). The filtrate was concentrated *in vacuo* to give imine **301** (1.39 g, 76%, lit.[122] 46%) as an orange solid which was used without further purification; mp. 84-86 °C; (lit.[122] mp. 86 °C); ^{1}H NMR (400 MHz) δ 2.27 (3H, s, CC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 6.75-6.79 (2H, m, Ar*H*), 6.90-6.94 (2H, m, Ar*H*), 7.42-7.48 (3H, m, Ar*H*), 7.96-8.00 (2H, m, Ar*H*). Data in agreement with that reported.[122]

3,4-Dihydroisoquinoline (268)[123]

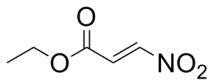


267

To a solution of 1,2,3,4-tetrahydroisoquinoline **266** (0.99 mL, 7.5 mmol) in Et_2O (70 mL) under N_2 was added NCS (1.10 g, 8.26 mmol, 1.1 equiv.) and the mixture stirred at rt for 15 h. To the solution was added H_2O (30 mL) and the layers separated. The aq. layer was extracted with Et_2O (3 x 20 mL) and the combined organics washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude chloro-tetrahydroisoquinoline **267** (1.40 g). To the crude chloro-tetrahydroquinoline **267** (1.40 g, 8.38 mmol) in CH_2Cl_2 (50 mL) under N_2 at 0 °C was added DBU (1.19

mL, 9.22 mmol, 1.1 equiv.). After 15 min the mixture was warmed to rt and stirred for a further 15 h. To the mixture was added H_2O (30 mL) and the layers separated. The aq. layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-70% EtOAc/hexanes) gave dihydroisoquinoline **268** (0.57 g, 58% over two steps, lit.[123] 94%) as a yellow solid; mp. 34-36 °C (lit.[123] mp. 35-36 °C); R_f 0.19 (70% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 2.76 (2H, t, *J* = 7.8, C*H*$_2$CH$_2$N), 3.76-3.80 (2H, m, CH$_2$C*H*$_2$N), 7.16 (1H, d, *J* = 7.2, Ar*H*), 7.29-7.33 (2H, m, Ar*H*), 7.37 (1H, td, *J* = 6.8, 2.0, Ar*H*), 8.35 (1H, s, C*H*N). Data in agreement with that reported.[123]

(*E*)-3-Nitroacrylic acid ethyl ester (141)[124]



141

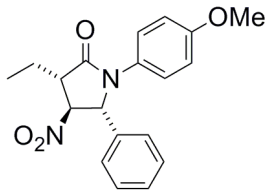
To a solution of ethyl glyoxylate **237** (24.0 mL of a 50% solution in toluene, 121 mmol) under N_2 was added nitromethane (60 mL) and Al_2O_3 (32.0 g). The mixture was stirred at rt for 15 h before being filtered and concentrated *in vacuo* to give crude nitro alcohol **236** (16.2 g) as a yellow oil; R_f 0.23 (50% EtOAc/hexanes). To a solution of crude nitro alcohol **236** (16.2 g, 99.4 mmol) in CH_2Cl_2 (100 mL) under N_2 at –20 °C was added Et_3N (41.5 mL, 298 mmol, 3.0 equiv.) dropwise. To the resulting solution was added methanesulfonyl chloride (23.0 mL, 298 mmol, 3.0 equiv.) dropwise over 45 min. The mixture was stirred at –20 °C for a further 1 h before H_2O (100 mL) was added and the layers separated. The aq. phase was washed with CH_2Cl_2 (3 x 50 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash column chromatography (10% EtOAc/hexanes) gave nitroalkene **141** (5.58 g, 39% over two steps, lit.[124] 75%) as a low melting yellow solid; mp. 37-39 °C (lit.[124] 39-40 °C); R_f 0.29 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 1.35 (3H, t, *J* = 7.1, C*H*$_3$), 4.32 (2H, q, *J* = 7.2, C*H*$_2$CH$_3$), 7.08 (1H, d, *J* = 13.5, *CH*CO$_2$Et), 7.68 (1H, d, *J* = 13.5, C*H*NO$_2$). Data in agreement with that reported.[124]

5.4.2 Synthesis of Pyrrolidinones

General Procedure B: Pyrrolidinone Formation

To a solution of nitroalkene **141** (100 mg, 0.69 mmol) in THF (3 mL) under N_2 was added $Cu(OTf)_2$ (12.4 mg, 34.0 μmol, 5 mol%). The mixture was cooled to –78 °C and diethylzinc (0.76 mL, 0.76 mmol, of a 1.0 M sol. in hexanes, 1.1 equiv.) was added dropwise over 1 min. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The dark mixture was re-cooled to –78 °C and the corresponding imine (1.38 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before a solution of TFA (180 μL, 2.41 mmol, 3.5 equiv.) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Sat. aq. $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aq. phase was extracted with Et_2O (3 x 20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave crude pyrrolidinone.

(3*S*, 4*S*, 5*R*)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one (223)[97]

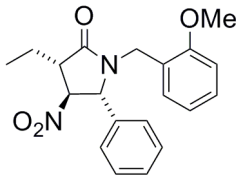


223

Racemic sample prepared by general procedure B. Enantioselective sample prepared by the following: A suspension of $Cu(OTf)_2$ (12.4 mg, 34.0 μmol, 5 mol%) and phosphoramidite **299** (18.2 mg, 34.0 μmol, 5 mol%) in Et_2O (3 mL) under N_2 was stirred at rt for 1 h. The mixture was cooled to –78 °C and nitroalkene **141** (100 mg, 690 μmol) was added, followed by diethylzinc (760 μL, 760 μmol of a 1 M sol. in hexanes, 1.1 equiv.) dropwise over 1 min. The orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The mixture was re-cooled to –78 °C and PMP-protected phenyl imine **227** (291 mg, 1.38 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before a solution of TFA (188 μL, 2.41 mmol, 3.5 equiv.) in THF (0.5 mL)

was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Sat. aq. $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aq. phase was extracted with Et_2O (3 x 20 mL) and the combined organics was washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford crude pyrrolidinone **223**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave **223** (196 mg, 84%, lit.[97] 63%) as a pale yellow solid; mp. 134-136 °C (lit.[97] mp. 135-137 °C); R_f 0.28 (20% Me_2CO/hexanes); $[\alpha]_D$ -34.9 (c 0.98, $CHCl_3$); ^{1}H NMR (500 MHz) δ 1.10 (3H, t, *J* = 7.5, CH_2CH_3), 1.83 (1H, ddq, *J* = 14.3, 8.2, 7.5, CH_2CH_3), 2.13 (1H, dqd, *J* = 14.3, 7.5, 4.8, CH_2CH_3), 3.32 (1H, ddd, *J* = 8.4, 6.8, 4.8, CHEt), 3.73 (3H, s, OCH_3), 4.81 (1H, dd, *J* = 6.8, 5.2, $CHNO_2$), 5.61 (1H, d, *J* = 5.3, CHPh), 6.80 (2H, m, ArH), 7.20-7.27 (4H, m, ArH), 7.31-7.34 (3H, m, ArH); HPLC (chiralcel OD-H 15 mm column with guard, 95:5 hexane/IPA, 1 mL min^{-1}) 32.8 min (minor), 45.0 min (major) measured 52% *ee*. Data in agreement with that reported.[97]

(3*S, 4*S**, 5*R**)-3-Ethyl-1-(2-methoxybenzyl)-4-nitro-5-phenylpyrrolidin-2-one (228)**

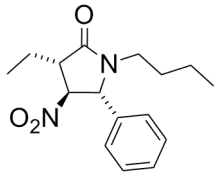


228

Prepared by general procedure B, except using Et_2O as the reaction solvent and 1.1 equiv. of imine. Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, OMB-protected phenyl imine **320** (0.70 g, 0.76 mmol) and TFA afforded crude pyrrolidinone **228**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave **228** (140 mg, 57%) as a pale yellow solid; mp. 100-102 °C; R_f 0.35 (20% Me_2CO/hexanes); IR υ_{max} 2976 (CH), 2938 (CH), 1697 (C=O), 1553 (NO_2), 1245 (C-O) cm^{-1}; ^{1}H NMR (500 MHz) δ 1.04 (3H, t, *J* = 7.5, CH_2CH_3), 1.75 (1H, ddq, *J* = 14.4, 8.3, 7.5, CH_2CH_3), 2.07 (1H, dqd, *J* = 14.2, 7.6, 4.6, CH_2CH_3), 3.17 (1H, ddd, *J* = 8.4, 6.7, 4.7, CHEt), 3.68 (3H, s, OCH_3), 3.78 (1H, d, *J* = 14.7, NCH_2Ar), 4.67 (1H, dd, *J* = 6.6, 5.3, $CHNO_2$), 4.80 (1H, d, *J* = 5.3, CHPh), 5.03 (1H, d, *J* = 14.7, NCH_2Ar), 6.76-6.89 (2H, m, ArH), 7.00 (1H, m, ArH), 7.07–7.13 (2H, m, ArH), 7.21-7.29 (1H, m, ArH), 7.35-7.44 (3H, m, ArH); ^{13}C NMR (125 MHz) δ 10.9 (CH_3), 23.1 (CH_2), 40.6

(*C*H_2Ar), 48.7 (*C*HEt), 55.0 (O*C*H_3), 64.4 (*C*HPh), 90.8 (*C*HNO_2), 110.3 (Ar), 120.6 (Ar), 122.8 (Cq), 126.9 (Ar), 129.1 (2 x Ar), 129.2 (Ar), 129.4 (Ar), 129.5 (Ar), 130.8 (Ar), 137.5 (Cq), 157.6 (Cq), 171.8 (C=O); *m/z* (ESI^+) 355 (100%, MH^+); HRMS: found 355.1651, $C_{20}H_{23}N_2O_4$ requires 355.1658; Anal. Cald. For $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.26, N, 7.90. Found C, 67.25, H, 6.22, N, 7.78%.

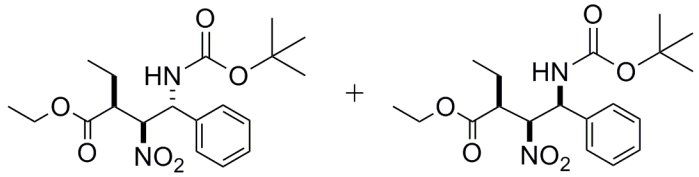
(3*S, 4*S**, 5*R**)-1-Butyl-3-ethyl-4-nitro-5-phenylpyrrolidin-2-one (229)**



229

Prepared by general procedure B, except using Et_2O as the reaction solvent. Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, *n*-butyl protected phenyl imine **319** (0.22 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **229**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave **229** (92 mg, 46%) as a pale yellow oil; R_f 0.44 (20% Me_2CO/hexanes); IR υ_{max} 2963 (CH), 2933 (CH), 1696 (C=O), 1557 (NO_2), 1458, 1421, 1368, 701 cm^{-1}; ^1H NMR (400 MHz) δ 0.86 (3H, t, *J* = 7.2, $(CH_2)_3CH_3$), 1.02 (3H, t, *J* = 7.4, $CHCH_2CH_3$), 1.17-1.33 (2H, m, $CH_2CH_2CH_3$), 1.35-1.44 (2H, m, $CH_2CH_2CH_3$), 1.72 (1H, ddq, *J* = 14.4, 8.2, 7.4, $CHCH_2CH_3$), 2.05 (1H, dqd, *J* = 14.0, 7.6, 4.8, $CHCH_2CH_3$), 2.58 (1H, ddd, *J* = 13.2, 7.6, 6.0, NCH_2CH_2), 3.14 (1H, ddd, *J* = 8.4, 6.8, 4.8, C*H*Et), 3.78 (1H, dt, *J* = 14.0, 8.0, NCH_2CH_2), 4.70 (1H, dd, *J* = 6.8, 5.4, C*H*NO_2), 5.03 (1H, d, *J* = 5.4, C*H*Ph), 7.18-7.23 (2H, m, Ar*H*), 7.38-7.46 (3H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 10.9 (CH_3), 13.7 (CH_3), 19.9 (CH_2), 23.1 (CH_2), 28.7 (CH_2), 40.7 (CH_2), 48.9 (*C*HEt), 64.3 (*C*HPh), 90.8 (*C*HNO_2), 126.9 (2 x Ar), 129.5 (Ar), 129.6 (2 x Ar), 136.9 (Cq), 171.6 (C=O); *m/z* (ESI^+) 291 (MH^+, 40%), 244 (M^+-NO_2, 100%), 245 (MH^+-NO_2, 50%); HRMS found 291.1709, $C_{16}H_{23}N_2O_3$ requires 291.1712.

(3*S, 4*S**, 5*R**)-4-*tert*-Butoxycarbonylamino-2-ethyl-3-nitro-4-phenylbutyric acid ethyl ester (233) and (2*S**, 3*S**, 4*S**)-4-*tert*-butoxycarbonylamino-2-ethyl-3-nitro-4-phenylbutyric acid ethyl ester (232)**

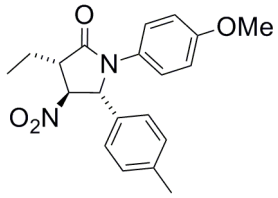


233 **232**

Prepared by general procedure B, except using Et_2O as the reaction solvent. Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, Boc-protected phenyl imine **321** (0.28 g, 1.40 mmol) and TFA afforded crude nitroamines. Purification by flash column chromatography (20% Me_2CO/hexanes) gave in order of elution: minor diastereoisomer **233** (23 mg, 8%) as a white solid; mp. 84-86 °C; R_f 0.33 (20% Me_2CO/hexanes); IR υ_{max} 2977 (CH), 2938 (CH), 1720 (C=O), 1557 (NO_2), 1494, 1367, 1249 (C-O), 1169 cm^{-1}; ^1H NMR (400 MHz) δ 0.96 (3H, t, *J* = 7.4, CH_2CH_3), 1.32 (3H, t, *J* = 7.2, OCH_2CH_3), 1.47 (9H, s, $C(CH_3)_3$), 1.60-1.67 (2H, m, CH_2CH_3), 3.20 (1H, ddd, *J* = 11.3, 7.4, 5.4, C*H*Et), 4.13-4.23 (1H, m, OCH_2CH_3), 4.24-4.33 (1H, m, OCH_2CH_3), 5.12 (1H, dd, *J* = 11.0, 3.8, C*H*NO_2), 5.35 (1H, dd, *J* = 10.4, 3.6, C*H*Ph), 5.91 (1H, d, *J* = 10.4, N*H*Boc), 7.20-7.38 (5H, m, Ar*H*); ^{13}C NMR (100 MHz) δ 10.2 (CH_3), 13.8 (CH_3), 23.8 (CH_2), 27.9 (3 x CH_3), 46.8 (*C*HEt), 53.3 (*C*HPh), 61.3 (CH_2), 80.0 (Cq), 92.4 (*C*HNO_2), 125.5 (2 x Ar), 128.0 (Ar), 128.6 (2 x Ar), 136.7 (Cq), 154.6 (C=O), 170.8 (C=O); *m/z* (CI^+) 381 (17%, MH^+), 234 (100%, MH^+-Boc-NO_2); HRMS: found 381.2032, $C_{19}H_{29}N_2O_6$ requires 381.2026. Major diastereoisomer **232** (146 mg, 56%) as a white solid; mp. 122-124 °C; R_f 0.28 (20% Me_2CO/hexanes); IR υ_{max} 2977 (CH), 2934 (CH), 1705 (C=O), 1555 (NO_2), 1367, 1241 (C-O), 1161, 1018 cm^{-1}; ^1H NMR (400 MHz) δ 0.93 (3H, t, *J* = 7.1, CH_2CH_3), 1.33 (3H, t, *J* = 7.4, OCH_2CH_3), 1.42 (9H, s, $C(CH_3)_3$), 1.63 (2H, sept, *J* = 7.2, CH_2CH_3), 2.99 (1H, app. dt, *J* = 9.7, 6.7, C*H*Et), 4.10-4.20 (1H, m, OCH_2CH_3), 4.24-4.31 (1H, m, OCH_2CH_3), 4.95 (1H, d, *J* = 9.4, N*H*Boc), 5.23 (1H, t, *J* = 9.4, C*H*NO_2), 5.32 (1H, t, *J* = 9.2, C*H*Ph), 7.20-7.27 (2H, m, Ar*H*), 7.30-7.38 (3H, m, Ar*H*); ^{13}C NMR (100 MHz) δ 10.5 (CH_3), 13.9 (CH_3), 22.4 (CH_2), 28.0 (3 x CH_3), 47.4 (*C*H), 56.2 (*C*H), 61.1 (CH_2), 80.3 (Cq), 91.7 (*C*H), 126.7 (2 x Ar), 128.5 (Ar), 128.7 (Ar),

129.4 (Ar), 136.6 (Cq), 154.3 (C=O), 171.8 (C=O); *m/z* (CI^+) 381 (47%, MH^+), 234 (100%, MH^+-$CO_2{}^t$Bu-NO_2); HRMS: found 381.2034, $C_{19}H_{29}N_2O_6$ requires 381.2026. Anal. Cald. For $C_{19}H_{28}N_2O_6$: C, 59.98, H, 7.42, N, 7.36. Found C, 59.90, H, 7.42, N, 7.27%.

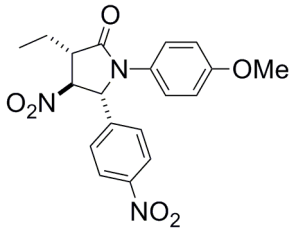
(3*S, 4*S**, 5*R**)- 3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(4-tolyl)-pyrrolidin-2-one (247)**



247

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 4-tolyl imine **322** (0.31 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **247**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **247** (146 mg, 60%) as an off white solid; mp. 104-106 °C; R_f 0.27 (20% Me_2CO/hexanes); IR υ_{max} 2966 (CH), 1706 (C=O), 1555 (NO_2), 1513, 1366, 1249 (C-O) cm^{-1}; ^{1}H NMR (600 MHz) δ 1.09 (3H, t, *J* = 7.5, CH_2CH_3), 1.83 (1H, ddq, *J* = 14.4, 7.3, 8.4, CH_2CH_3), 2.14 (1H, dqd, *J* = 14.2, 7.5, 4.8, CH_2CH_3), 2.31 (3H, s, ArCH_3), 3.32 (1H, ddd, *J* = 8.5, 6.8, 4.8, C*H*Et), 3.74 (3H, s, OCH_3), 4.79 (1H, dd, *J* = 6.8, 5.3, C*H*NO_2), 5.57 (1H, d, *J* = 5.3, C*H*Ar), 6.79-6.81 (2H, m, Ar*H*), 7.09-7.15 (2H, m, Ar*H*), 7.24-7.28 (2H, m, Ar*H*), 7.29-7.34 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 10.5 (CH_3), 20.8 (ArCH_3), 23.0 (CH_2), 48.9 (Et*C*H), 55.0 (OCH_3), 65.4 (*C*HAr), 90.3 (*C*HNO_2), 113.8 (2 x Ar), 124.6 (2 x Ar), 126.2 (2 x Ar), 129.2 (Cq), 129.7 (2 x Ar), 133.9 (Cq), 138.8 (Cq), 157.2 (Cq), 170.6 (C=O); *m/z* (ESI^-) 353 (70%, M-H^-); HRMS: found 353.1513, $C_{20}H_{21}N_2O_4$ requires 353.1501; Anal. Cald. For $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.26, N, 7.90. Found C, 67.95, H, 6.18, N, 7.56%.

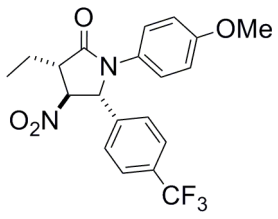
(3*S, 4*S**, 5*R**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(4-nitrophenyl)-pyrrolidin-2-one (248)**



248

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 4-nitro imine **241** (0.26 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **248**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **248** (0.14 g, 54%) as an off white solid; mp. 167-169 °C; R_f 0.16 (20% Me_2CO/hexanes); IR υ_{max} 2968 (CH), 2950 (CH), 1701 (C=O), 1610, 1555 (NO_2), 1510, 1343, 1246 (C-O), 1032 cm^{-1}; ^1H NMR (400 MHz) δ 1.09 (3H, t, *J* = 7.6, CH_2CH_3), 1.85 (1H, app. dquint, *J* = 14.6, 7.4, CH_2CH_3), 2.13 (1H, dqd, *J* = 14.4. 7.6, 4.8, CH_2CH_3), 3.38 (1H, app. td, *J* = 7.8, 4.8, C*H*Et), 3.72 (3H, s, OCH_3), 4.76 (1H, dd, *J* = 7.1, 5.8, $CHNO_2$), 5.76 (1H, d, *J* = 5.8, C*H*Ar), 6.77-6.81 (2H, m, Ar*H*), 7.20-7.24 (2H, m, Ar*H*), 7.42-7.44 (2H, m, Ar*H*), 8.61-8.20 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 10.7 (CH_3), 23.2 (CH_2), 48.7 (*C*HEt), 55.4 (OCH_3), 64.7 (*C*HAr), 89.6 ($CHNO_2$), 114.6 (2 x Ar), 124.7 (2 x Ar), 124.9 (2 x Ar), 127.0 (2 x Ar), 128.8 (Cq), 144.4 (Cq), 148.4 (Cq), 157.9 (Cq), 170.7 (C=O); *m/z* (ESI$^-$) 384 (30% M-H$^-$), 366 (100%, M-H$^-$(-H_2O)); HRMS: found 384.1178, $C_{19}H_{18}N_3O_6$ requires 384.1196; Anal. Cald. For $C_{19}H_{19}N_3O_6$: C, 59.22, H, 4.97, N, 10.90. Found C, 58.88, H, 4.94, N, 10.75%.

(3*S, 4*S**, 5*R**)- 3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(4-trifluoromethylphenyl)-pyrrolidin-2-one (249)**

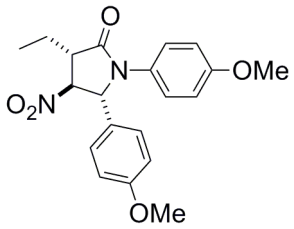


249

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 4-trifluoromethyl imine **242** (0.39 g, 1.40 mmol) and TFA afforded

crude pyrrolidinone **249**. Purification by flash column chromatography (20% Me_2CO/hexanes) afforded pyrrolidinone **249** (0.20 g, 70%) as a pale yellow solid; mp. 140-142 °C; R_f 0.20 (20% Me_2CO/hexanes); IR υ_{max} 2969 (CH), 2939 (CH), 1704 (C=O), 1555 (NO_2), 1512, 1323, 1248 (C-O), 1166, 1122, 1112, 1067 cm^{-1}; ^1H NMR (600 MHz) δ 1.09 (3H, t, *J* = 7.5, CH_2CH_3), 1.83 (1H, ddq, *J* = 14.4, 7.5, 7.2 CH_2CH_3), 2.12 (1H, dqd, *J* = 14.3, 7.5, 4.8, CH_2CH_3), 3.36 (1H, ddd, *J* = 14.2, 7.6, 4.7, C*H*Et), 3.73 (3H, s, OCH_3), 4.76 (1H, dd, *J* = 6.6, 5.5, $CHNO_2$), 5.71 (1H, d, *J* = 5.7, C*H*Ar), 6.80 (2H, d, *J* = 9.0, Ar*H*), 7.24 (2H, d, *J* = 9.0, Ar*H*), 7.34 (2H, d, *J* = 8.4, Ar*H*), 7.60 (2H, d, *J* = 7.8, Ar*H*); ^{13}C NMR (125 MHz) δ 10.8 (CH_3), 23.3 (CH_2), 49.0 (Et*C*H), 55.4 (OCH_3), 65.1 (*C*HAr), 90.0 ($CHNO_2$), 114.5 (3 x Ar), 123.7 (1C, q, *J* = 270.9, CF_3), 124.7 (2 x Ar), 126.6 (Ar), 127.2 (2 x Ar), 129.1 (Cq), 131.4 (1C, q, *J* = 32.4, CCF_3), 141.5 (Cq), 157.8 (Cq), 170.9 (C=O); ^{19}F NMR (282 MHz) δ -63.2 (3F, s, CF_3); *m/z* (FAB^+) 409 (100%, MH^+), 363 (35%, MH^+-NO_2); HRMS found 409.1385, $C_{20}H_{20}F_3N_2O_4$ requires 409.1375; Anal. Cald. For $C_{20}H_{19}F_3N_2O_4$: C, 58.82, H, 4.69, N, 6.86. Found C, 58.92, H, 4.65, N, 6.66%.

(3*S, 4*S**, 5*R**)-3-Ethyl-1,5-bis-(4-methoxyphenyl)-4-nitropyrrolidin-2-one (250)**

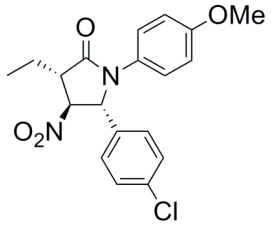


250

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 4-methoxy imine **243** (0.28 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **250**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **250** (0.21 g, 47%) as an off white solid; mp. 88-90 °C; R_f 0.23 (20% Me_2CO/hexanes); IR υ_{max} 2966 (CH), 2936 (CH), 2838 (CH), 1704 (C=O), 1553 (NO_2), 1512, 1366, 1248 (C-O), 1177, 1031 cm^{-1}; ^1H NMR (400 MHz) δ 1.09 (3H, t, *J* = 7.5, CH_2CH_3), 1.83 (1H, app. dquint, *J* = 14.8, 7.5, CH_2CH_3), 2.13 (1H, dqd, *J* = 14.2, 7.5, 4.7, CH_2CH_3), 3.31 (1H, ddd, *J* = 8.2, 7.1, 4.7, C*H*Et), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.79 (1H, dd, *J* = 7.0, 5.5, $CHNO_2$), 5.53 (1H, d, *J* = 5.4, C*H*Ar), 6.78-6.80 (2H, m, Ar*H*), 6.82-6.85 (2H, m, Ar*H*), 7.11-7.13 (2H, m, Ar*H*), 7.21-7.27 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 10.9 (CH_3), 23.3

(CH_2), 49.2 (*C*HEt), 55.3 (O*C*H_3), 55.4 (O*C*H_3), 65.6 (*C*HAr), 90.9 (*C*HNO_2), 114.2 (2 x Ar), 114.8 (2 x Ar), 125.2 (2 x Ar), 128.0 (2 x Ar), 129.0 (Cq), 129.5 (Cq), 157.6 (Cq), 160.1 (Cq), 170.9 (C=O); *m/z* (FAB^+) 371 (100%, MH^+), 324 (30%, M^+-NO_2); HRMS: found 371.1598, $C_{20}H_{23}N_2O_5$ requires 371.1607.

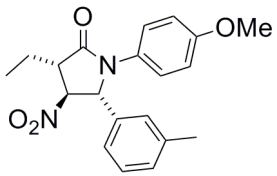
(3*S, 4*S**, 5*R**)-5-(4-Chlorophenyl)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-pyrrolidin-2-one (251)**



251

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 4-chloro imine **323** (0.34 g, 1.38 mmol) and TFA afforded crude pyrrolidinone **251** Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **251** (0.19 g, 74%) as an off white solid; mp. 136-138 °C; R_f 0.34 (20% Me_2CO/hexanes); IR υ_{max} 2967 (CH), 2936 (CH), 1702 (C=O), 1554 (NO_2), 1510, 1246 (C-O), 728 (C-Cl) cm^{-1}; ^1H NMR (400 MHz) δ 1.09 (3H, t, *J* = 7.4, CH_2CH_3), 1.84 (1H, app. dquint, *J* = 14.9, 7.5, CH_2CH_3), 2.12 (1H, dqd, *J* = 14.3, 7.5, 4.7, CH_2CH_3), 3.33 (1H, ddd, *J* = 8.1, 7.1, 4.7, C*H*Et), 3.74 (3H, s, OCH_3), 4.77 (1H, dd, *J* = 7.0, 5.5, C*H*NO_2), 5.59 (1H, d, *J* = 5.5, C*H*Ar), 6.78-6.82 (2H, m, Ar*H*), 7.15-7.17 (2H, m, Ar*H*), 7.20-7.23 (2H, m, Ar*H*), 7.29-7.34 (2H, m, Ar*H*); ^{13}C NMR (100 MHz) δ 10.4 (CH_3), 22.9 (CH_2), 48.6 (*C*HEt), 55.2 (OCH_3), 64.8 (*C*HAr), 89.9 (*C*HNO_2), 113.9 (2 x Ar), 124.6 (2 x Ar), 127.7 (2 x Ar), 128.7 (Cq), 129.4 (2 x Ar), 134.8 (Cq), 135.4 (Cq), 157.4 (Cq), 170.5 (C=O); *m/z* (ESI^-) 373 (78%, M-H^-); HRMS: found 373.0944, $C_{19}H_{18}N_2O_4Cl$ requires 373.0995; Anal. Cald. For $C_{19}H_{19}N_2O_4Cl$: C, 60.88, H, 5.11, N, 7.47. Found C, 60.76, H, 5.07, N, 7.20%.

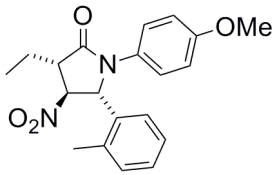
(3*S, 4*S**, 5*R**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(3-tolyl)-pyrrolidin-2-one (252)**



252

Prepared by general procedure B: **141** (100 mg, 690 μmol), diethylzinc, PMP-protected 3-tolyl imine **324** (310 mg, 1.40 mmol) and TFA afforded crude pyrrolidinone **252**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **252** (175 mg, 72%) as an off white solid; mp. 109-111 °C; R_f 0.32 (20% Me_2CO/hexanes); IR υ_{max} 2966 (CH), 2938 (CH), 1704 (C=O), 1556 (NO_2), 1517, 1367, 1248 (C-O), 1182, 1032 cm^{-1}; ^1H NMR (400 MHz) δ 1.09 (3H, t, *J* = 7.4, CH_2CH_3), 1.82 (1H, app. dquint, *J* = 14.3, 7.5, CH_2CH_3), 2.13 (1H, dqd, *J* = 14.2, 7.5, 4.8, CH_2CH_3), 2.31 (3H, s, $ArCH_3$), 3.31 (1H, ddd, *J* = 8.4, 6.8, 4.7, CHEt), 3.74 (3H, s, OCH_3), 4.79 (1H, dd, *J* = 6.8, 5.4, $CHNO_2$), 5.56 (1H, d, *J* = 5.4, CHAr), 6.78-6.82 (2H, m, ArH), 7.08-7.15 (4H, m, ArH), 7.23-7.27 (2H, m, ArH); ^{13}C NMR (125 MHz) δ 10.5 (CH_3), 20.8 ($ArCH_3$), 23.0 (CH_2), 48.9 (EtCH), 55.0 (OCH_3), 65.4 (CHAr), 90.3 ($CHNO_2$), 113.8 (2 x Ar), 124.6 (2 x Ar), 126.2 (2 x Ar), 129.2 (Cq), 129.7 (2 x Ar), 133.9 (Cq), 138.8 (Cq), 157.2 (Cq), 170.6 (C=O); *m/z* (ESI^+) 355 (10%, MH^+), 377 (25%, MNa^+), 308 (100%, M^+-NO_2); HRMS: found 377.1471, $C_{20}H_{22}N_2O_4Na$ requires 377.1477.

(3*S, 4*S**, 5*R**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(2-tolyl)-pyrrolidin-2-one (253)**

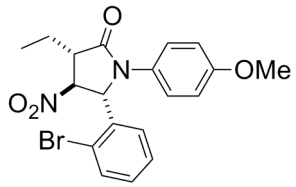


253

Prepared by general procedure B: **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 2-tolyl imine **245** (0.31 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **253**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **253** (0.11 g, 46%) as an off white solid; mp. 102-104 °C; R_f 0.38 (20% Me_2CO/hexanes); IR υ_{max} 2968 (CH), 2935 (CH), 1705

(C=O), 1555 (NO_2), 1513, 1367, 1249 (C-O) cm^{-1}; ^1H NMR (400 MHz, 60 °C, signals at 25 °C appear broad due to atropisomerism) δ 1.08 (3H, t, *J* = 7.4, CH_2CH_3), 1.77 (1H, ddq, *J* = 14.3, 8.6, 7.3, CH_2CH_3), 2.15 (1H, dqd, *J* = 14.3, 7.6, 5.2, CH_2CH_3), 2.36 (3H, s, $ArCH_3$), 3.25 (1H, app. dt, *J* = 8.7, 5.2, CHEt), 3.75 (3H, s, OCH_3), 4.81 (1H, dd, *J* = 5.3, 4.3, $CHNO_2$), 5.91 (1H, d, *J* = 4.3, CHAr), 6.78-6.80 (2H, m, ArH), 7.11 (1H, m, ArH), 7.14-7.21 (3H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz) δ 11.4 (CH_3), 19.3 ($ArCH_3$), 23.9 (CH_2), 50.3 (CHEt), 55.4 (OCH_3), 62.6 (CHAr), 89.6 ($CHNO_2$), 114.3 (2 x Ar), 124.4 (3 x Ar), 125.7 (Cq), 127.0 (Ar), 128.9 (Ar), 129.8 (Cq), 131.6 (Ar), 135.7 (Cq), 157.6 (Cq), 171.5 (C=O); *m/z* (FAB^+) 377 (15%, MNa^+), 354 (5%, M^+), 176 (100%, M^+-178); HRMS: found 377.1464, $C_{20}H_{22}N_2O_4Na$ requires 377.1472; Anal. Cald. For $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.26, N, 7.90. Found C, 67.32, H, 6.21, N, 7.84%.

(3*S, 4*S**, 5*R**)-5-(2-Bromophenyl)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-pyrrolidin-2-one (254)**

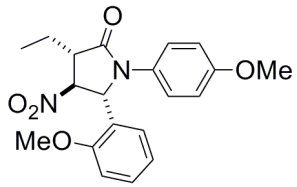


254

Prepared by general procedure B, except 1.1 equiv. of imine was used. Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 2-bromo imine **325** (0.22 g, 0.76 mmol) and TFA afforded crude pyrrolidinone **254**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **254** (0.16 g, 56%) as an off white solid; mp. 132-134 °C; R_f 0.23 (20% Me_2CO/hexanes); IR υ_{max} 2967 (CH), 2936 (CH), 2879 (CH), 2838 (C-H), 1704 (C=O), 1554 (NO_2), 1511, 1365, 1247 (C-O), 1177, 1027 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$, 100 °C, signals at 25 °C appear broad due to atropisomerism) δ 1.00 (3H, t, *J* = 7.2, CH_2CH_3), 1.73 (1H, app. dquint, *J* = 14.8, 7.6, CH_2CH_3), 1.92 (1H, dqd, *J* = 12.0, 7.2, 5.6, CH_2CH_3), 3.28 (1H, ddd, *J* = 12.0, 8.0, 6.4, CHEt), 3.63 (3H, s, OCH_3), 5.11 (1H, app. t, *J* = 5.6, $CHNO_2$), 6.00 (1H, d, *J* = 5.2, CHAr), 6.76-6.80 (2H, m, ArH), 7.14-7.23 (2H, m, ArH), 7.23-7.34 (2H, m, ArH), 7.53 (2H, m, ArH); ^{13}C NMR (125 MHz) δ 11.6 (CH_3), 24.4 (CH_2), 51.2 (CHEt), 55.5 (OCH_3), 64.7 (CHAr), 88.5 ($CHNO_2$), 114.4 (2 x Ar), 123.2 (Cq), 124.0 (Ar), 127.5 (Cq), 128.3 (Cq), 129.7 (2 x Ar), 130.6 (Ar), 133.9 (Ar), 136.3

(Ar), 157.6 (Cq), 171.7 (C=O); *m/z* (ESI^+) 419 (5% MH^+), 372 (100%, M^+-NO_2); HRMS found 419.0624, $C_{19}H_{20}N_2O_4Br$ requires 419.0606; Anal. Cald. For $C_{19}H_{19}BrN_2O_4$: C, 54.43, H, 4.57, N, 6.68. Found C, 54.67, H, 4.56, N 6.65%.

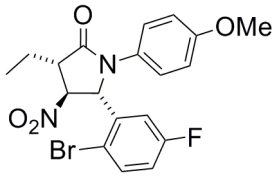
(3*S, 4*S**, 5*R**)-3-Ethyl-1-(4-methoxyphenyl)-5-(2-methoxyphenyl)-4-nitro-pyrrolidin-2-one (255)**



255

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected *o*-methoxy imine **245** (0.32 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **255**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **255** (125 mg, 49%) as an off white solid; mp. 114-116 °C; R_f 0.27 (20% Me_2CO/hexanes); IR υ_{max} 2967 (CH), 2937 (CH), 2838 (CH), 1701 (C=O), 1553 (NO_2), 1512, 1244 (C-O), 1027 cm^{-1}; ^1H NMR (400 MHz) δ 1.06 (3H, t, *J* = 7.5, CH_2CH_3), 1.69 (1H, ddq, *J* = 14.2, 9.1, 7.3, CH_2CH_3), 2.09 (1H, dqd, *J* = 14.1, 7.8, 4.7, CH_2CH_3), 3.15 (1H, app. dt, *J* = 9.4, 4.9, C*H*Et), 3.73 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.89 (1H, app. t, *J* = 4.4, $CHNO_2$), 5.92 (1H, d, *J* = 4.0, *CH*Ar), 6.78-6.82 (2H, m, Ar*H*), 6.89 (2H, d, *J* = 8.0, Ar*H*), 7.05 (1H, dd, *J* = 7.6, 1.6, Ar*H*), 7.25-7.29 (1H, m, Ar*H*), 7.33-7.37 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 11.4 (CH_3), 24.0 (CH_2), 50.6 (*C*HEt), 55.5 (OCH_3), 55.5 (OCH_3), 62.3 (*C*HAr), 88.8 ($CHNO_2$), 111.0 (2 x Ar), 114.2 (2 x Ar), 120.9 (Ar), 124.4 (Ar), 124.9 (Cq), 128.5 (Ar), 130.1 (Cq), 130.2 (Ar), 156.7 (Cq), 157.4 (Cq), 171.7 (C=O); *m/z* (CI^+) 370 (100%, M^+); HRMS found 370.1515, $C_{20}H_{22}N_2O_5$ requires 370.1523.

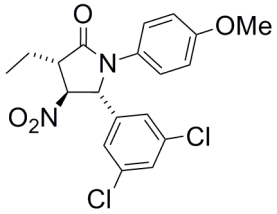
(3*S, 4*S**, 5*R**)-5-(2-Bromo-5-fluorophenyl)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-pyrrolidin-2-one (256)**



262

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 2-bromo-5-fluoro-phenyl imine **326** (0.43 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **256**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **256** (169 mg, 56%) as a white solid; mp. 150-152 °C; R_f 0.20 (20% Me_2CO/hexanes); IR υ_{max} 2968 (CH), 2838 (CH), 1709 (C=O), 1558 (NO_2), 1513, 1466, 1387, 1367, 1250 (C-O), 1031 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$, 100 °C, signals at 25 °C appeared broad due to atropisomerism) δ 0.68 (3H, t, *J* = 7.5, CH_2CH_3), 1.43 (1H, app. dquint, *J* = 14.8, 7.4, CH_2CH_3), 1.61 (1H, app. dquint, *J* = 13.2, 6.5, CH_2CH_3), 2.97 (1H app. q, *J* = 6.8, CHEt), 3.32 (3H, s, OCH_3), 4.87 (1H, app. t, *J* = 6.3, $CHNO_2$), 5.66 (1H, d, *J* = 5.5, CHAr), 6.46 (2H, d, *J* = 8.8, ArH), 6.69-6.74 (1H, m, ArH), 6.87 (3H, d, *J* = 8.8, ArH), 7.24 (1H, dd, *J* = 8.4, 5.2, ArH); ^{13}C NMR (125 MHz) δ 11.6 (CH_3), 24.5 (CH_2), 51.0 (CHEt), 55.5 (OCH_3), 64.5 (CHAr), 88.3 ($CHNO_2$), 114.5 (3 x Ar), 117.2 (Cq), 118.1 (1C, d, *J* = 22.0, ArCF), 124.0 (2 x Ar), 129.3 (Cq), 135.3 (Ar), 138.7 (Cq), 157.8 (Cq), 162.3 (1C, d, *J* = 248.5, CF), 171.5 (C=O); ^{19}F NMR (282 MHz) δ -111.8 (1F, s, CF); *m/z* (EI^+) 436 (100%, M^+); HRMS found 436.0424, $C_{19}H_{18}N_2O_4BrF$ requires 436.0429; Anal. Cald. For $C_{19}H_{18}N_2O_4BrF$: C, 52.19, H, 4.15, N, 6.41. Found C, 52.00, H, 4.11, N, 6.25%.

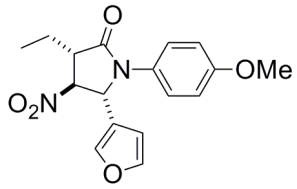
(3*S, 4*S**, 5*R**)-5-(3,5-Dichlorophenyl)-3-ethyl-1-(4-methoxyphenyl)-4-nitro-pyrrolidin-2-one (257)**



257

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 3,5-dichlorophenyl imine **246** (0.39 g, 1.4 mmol) and TFA afforded crude pyrrolidinone **257**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **257** (0.23 g, 83%) as a white solid; mp. 70-72 °C, R_f 0.14 (20% Me_2CO/hexanes); IR υ_{max} 2968 (CH), 2838 (CH), 1707 (C=O), 1557 (NO_2), 1513, 1440, 1386, 1366, 1249 (C-O) cm^{-1}; ^1H NMR (400 MHz) δ 1.11 (3H, t, *J* = 7.4, CH_2CH_3), 1.83 (1H, app. dquint, *J* = 14.8, 7.4, CH_2CH_3), 2.15 (1H, dqd, *J* = 15.1, 7.6, 4.9, CH_2CH_3), 3.33 (1H, ddd, *J* = 8.2, 7.0, 4.8, C*H*Et), 3.77 (3H, s, OCH_3), 4.74 (1H, dd, *J* = 7.0, 5.4, C*H*NO_2), 5.56 (1H, d, *J* = 5.5, C*H*Ar), 6.82-6.86 (2H, m, Ar*H*), 7.11 (2H, d, *J* = 2.0, Ar*H*), 7.20-7.24 (2H, m, Ar*H*), 7.31 (1H, t, *J* = 2.0, Ar*H*); ^{13}C NMR (125 MHz) δ 10.9 (CH_3), 23.4 (CH_2), 48.9 (*C*HEt), 55.5 (OCH_3), 64.7 (*C*HAr), 89.8 (*C*HNO_2), 114.6 (2 x Ar), 124.9 (2 x Ar), 125.3 (2 x Ar), 128.8 (Cq), 129.7 (Ar), 136.3 (2 x *C*-Cl), 140.9 (Cq), 158.0 (Cq), 170.8 (C=O); *m/z* (ESI^+) 408 (100%, M^+), 363 (78%, M^+-NO_2); HRMS found 408.0636, $C_{19}H_{18}N_2O_4Cl_2$ requires 408.0638; Anal. Cald. For $C_{19}H_{18}N_2O_4Cl_2$: C, 55.76, H, 4.43, N, 6.84. Found C, 55.44, H, 4.36, N, 6.74%.

(3*S, 4*S**, 5*R**)-3-Ethyl-5-(fur-3-yl)-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one (258)**

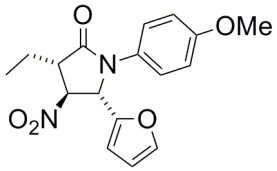


258

Prepared by general procedure B: Nitroalkene **141** (90.0 g, 620 mmol), diethylzinc, PMP-protected 3-furyl imine **327** (250 mg, 1.24 mmol) and TFA afforded crude pyrrolidinone **258**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave **258** (143 mg, 70%) as an orange solid; mp. 116-118 °C; R_f 0.25 (20% Me_2CO/hexanes); IR υ_{max} 2968 (CH), 2938 (CH), 2884 (CH), 1702 (C=O), 1555 (NO_2), 1512, 1366, 1248 (C-O), 1024 cm^{-1}; ^1H NMR (400 MHz) δ 1.11 (3H, t, *J* = 7.5, CH_2CH_3), 1.85 (1H, app. dquint, *J* = 14.8, 7.4, CH_2CH_3), 2.13 (1H, dqd, *J* = 14.2, 7.4, 4.7, CH_2CH_3), 3.29 (1H ddd, *J* = 8.2, 7.1, 4.8, C*H*Et), 3.76 (3H, s, OCH_3), 4.84 (1H, dd, *J* = 7.0, 5.6, C*H*NO_2), 5.55 (1H, d, *J* = 5.5, C*H*fur), 6.25 (1H, m, fur*H*), 6.81-6.86 (2H, m, Ar*H*), 7.14-7.21 (2H, m, Ar*H*), 7.33 (1H, s, fur*H*), 7.38

(1H, t, *J* = 1.6, fur*H*); ^{13}C NMR (125 MHz) δ 10.8 (*C*H$_3$), 23.3 (*C*H$_2$), 49.0 (*C*HEt), 55.5 (O*C*H$_3$), 58.4 (*C*Hfur), 89.5 (*C*HNO$_2$), 107.8 (fur), 114.6 (2 x Ar), 122.4 (Cq), 125.8 (2 x Ar), 129.0 (Cq), 141.4 (fur), 144.8 (fur), 158.1 (Cq), 170.6 (C=O); *m/z* (CI$^+$) 331 (100%, MH$^+$); HRMS found 331.1294, $C_{17}H_{19}N_2O_5$ requires 331.1291; Anal. Cald. For $C_{17}H_{18}N_2O_5$: C, 61.81, H, 5.49, N, 8.48. Found C, 61.62, H, 5.41, N, 8.35%.

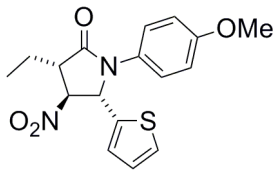
(3*S, 4*S**, 5*S**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(fur-2-yl)-pyrrolidin-2-one (259)**



259

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected 2-furyl imine **328** (0.28 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **259**. Purification by flash column chromatography (20% Me$_2$CO/hexanes) gave pyrrolidinone **259** (0.16 g, 68%) as an off white solid; mp. 87-88 °C; R$_f$ 0.33 (20% Me$_2$CO/hexanes); IR υ$_{max}$ 2967 (CH), 2937 (CH), 1703 (C=O), 1556 (NO$_2$), 1513, 1385, 1369, 1248 (C-O) cm^{-1}; ^{1}H NMR (400 MHz) δ 1.15 (3H, t, *J* = 7.6, CH$_2$C*H$_3$*), 1.93 (1H, ddq, *J* = 14.4, 8.5, 7.4, C*H*$_2$CH$_3$), 2.17 (1H, dqd, *J* = 14.2, 7.6, 4.9, C*H*$_2$CH$_3$), 3.24 (1H, ddd, *J* = 8.7, 5.9, 4.9, C*H*Et), 3.77 (3H, s, OC*H$_3$*), 5.12 (1H, dd, *J* = 5.9, 4.9, C*H*NO$_2$), 5.55 (1H, d, *J* = 4.7, C*H*fur), 6.27-6.30 (2H, m, fur*H*), 6.83-6.85 (2H, m, Ar*H*), 7.07–7.10 (2H, m, Ar*H*), 7.46 (1H, m, fur*H*); ^{13}C NMR (125 MHz) δ 11.0 (*C*H$_3$), 23.3 (*C*H$_2$), 49.3 (*C*HEt), 55.5 (O*C*H$_3$), 60.3 (*C*Hfur), 86.7 (*C*HNO$_2$), 110.9 (fur), 111.5 (fur), 114.4 (2 x Ar), 126.6 (2 x Ar), 128.8 (Cq), 143.8 (fur), 148.1 (Cq), 158.6 (Cq), 170.8 (C=O); *m/z* (ESI$^+$) 353 (100%, MNa$^+$), 331 (81%, MH$^+$), 284 (78%, M$^+$-NO$_2$); HRMS: found 353.1125, $C_{17}H_{18}N_2O_5Na$ requires 353.1113.

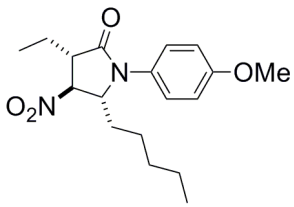
(3*S, 4*S**, 5*S**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-(thiophen-2-yl)-pyrrolidin-2-one (260)**



260

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected thiophene imine **329** (0.30 g, 1.4 mmol) and TFA afforded crude pyrrolidinone **260**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **260** (0.15 g, 64%) as an off white solid; mp. 90-92 °C; R_f 0.32 (20% Me_2CO/hexanes); IR υ_{max} 2967 (CH), 2936 (CH), 1701 (C=O), 1553 (NO_2), 1511, 1362, 1246 (C-O), 1030 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (3H, t, *J* = 7.4, CH_2CH_3), 1.91 (1H, app. dquint, *J* = 15.0, 7.4, CH_2CH_3), 2.16 (1H, dqd, *J* = 14.2, 7.5, 5.2, CH_2CH_3), 3.29 (1H, ddd, *J* = 8.1, 6.8, 4.9, C*H*Et), 3.75 (3H, s, OCH_3), 4.94 (1H, dd, *J* = 6.4, 5.4, C*H*NO_2), 5.89 (1H, d, *J* = 5.1, C*H*Ar), 6.83 (2H, app. d, *J* = 8.8, Ar*H*), 6.91 (1H, m, Ar*H*), 7.01 (1H, m, Ar*H*), 7.23 (2H, app. d, *J* = 9.2, Ar*H*), 7.27 (1H, d, *J* = 4.4, Ar*H*); ^{13}C NMR (125 MHz) δ 10.8 (CH_3), 23.5 (CH_2), 49.2 (*C*HEt), 55.4 (OCH_3), 62.0 (*C*HAr), 90.6 (*C*HNO_2), 114.6 (2 x Ar), 125.9 (2 x Ar), 127.0 (Ar), 127.3 (Ar), 127.8 (Ar), 129.0 (Cq), 140.6 (Cq), 158.1 (Cq), 170.5 (C=O); *m/z* (ESI^+) 369 (90%, MNa^+), 300 (100%, M^+-NO_2); HRMS: found 369.0888, $C_{17}H_{18}N_2O_4NaS$ requires 369.0885; Anal. Cald. For $C_{17}H_{18}N_2O_4S$: C, 58.94, H, 5.24, N, 8.09. Found C, 58.84, H, 5.19, N, 8.04%.

(3*S, 4*S**, 5*R**)-3-Ethyl-1-(4-methoxyphenyl)-4-nitro-5-pentylpyrrolidin-2-one (261)**

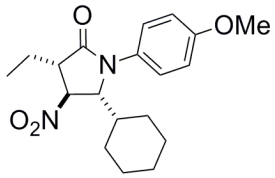


261

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected *n*-pentyl imine **330** (0.28 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **261**. Purification by flash column chromatography (20%

Me_2CO/hexanes) gave pyrrolidinone **261** (88 mg, 38%) as an orange oil; R_f 0.29 (20% Me_2CO/hexanes); IR υ_{max} 2958 (CH), 2861 (CH), 1699 (C=O), 1552 (NO_2), 1511, 1247 (C-O), 1032 cm^{-1}; ^1H NMR (600 MHz) δ 0.82 (3H, t, *J* = 6.9, $(CH_2)_4CH_3$), 1.10 (3H, t, *J* = 7.4, CH_2CH_3), 1.16-1.30 (6H, m, $(CH_2)_3CH_3$), 1.44-1.50 (1H, m, $CH_2(CH_2)_3$), 1.73-1.81 (2H, m, CH_2CH_3 + $CH_2(CH_2)_3$), 2.09 (1H, dqd, *J* = 15.0, 7.6, 4.8, CH_2CH_3), 3.19 (1H ddd, *J* = 8.7, 6.0, 5.0, CHEt), 3.81 (3H, s, OCH_3), 4.48 (1H, ddd, *J* = 8.5, 4.5, 3.5, CH*n*-Pn), 4.71 (1H, dd, *J* = 5.9, 5.2, $CHNO_2$), 6.92-6.94 (2H, m, Ar*H*), 7.20-7.21 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 11.0 (CH_3), 13.9 (CH_3) 22.4 (CH_2), 23.6 (CH_2), 23.7 (CH_2), 31.4 (CH_2), 32.5 (CH_2), 49.5 (CHEt), 55.6 (OCH_3), 62.5 (CH*n*-Pn), 87.4 ($CHNO_2$), 114.7 (2 x Ar), 126.6 (2 x Ar), 128.9 (Cq), 158.5 (Cq), 170.8 (C=O), *m/z* (CI^+) 335 (100%, MH^+); HRMS found 335.1962, $C_{18}H_{27}N_2O_4$ requires 335.1971.

(3*S, 4*S**, 5*R**)-5-Cyclohexyl-3-ethyl-1-(4-methoxyphenyl)-4-nitro-pyrrolidin-2-one (263)**

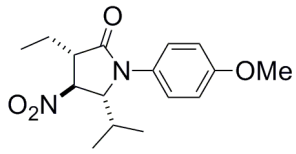


263

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected cyclohexyl imine **331** (0.30 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **263**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **263** (0.15 g, 62%) as an off white solid; mp. 122-124 °C; R_f 0.35 (20% Me_2CO/hexanes); IR υ_{max} 2929 (CH), 2855 (CH), 1698 (C=O), 1555 (NO_2), 1512, 1450, 1366, 1248 (C-O), 1033 cm^{-1}; ^1H NMR (600 MHz) δ 0.81 (1H, dq, *J* = 12.4, 3.3, *Cy*), 0.98 (1H, q, *J* = 12.6, *Cy*), 1.10 (3H, t, *J* = 7.4, CH_2CH_3), 1.05-1.20 (2H, m, *Cy*), 1.51 (2H, d, *J* = 8.0, *Cy*), 1.64-1.74 (5H, m, CH_2CH_3 + 4*Cy*), 2.10 (1H, dqd, *J* = 9.5, 7.6, 4.8, CH_2CH_3), 3.11 (1H, ddd, *J* = 9.4, 6.0, 4.8, CHEt), 3.83 (3H, s, OCH_3), 4.51 (1H, app. t, *J* = 4.2, $CHNO_2$), 4.81 (1H, app. t, *J* = 5.4, CHCy), 6.94 (2H, m, Ar*H*), 7.23 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 11.2 (CH_3), 23.4 (CH_2), 25.6 (Cy), 25.8 (Cy), 26.1 (Cy), 26.2 (Cy), 28.5 (Cy), 38.1 (CyCH), 50.0 (CHEt), 55.6 (OCH_3), 66.8 ($CHNO_2$), 84.4 (CHCy), 114.7 (2 x Ar), 126.6 (2 x Ar), 129.0 (Cq), 158.4 (Cq), 171.0 (C=O); *m/z* (FAB^+) 369 (100% MNa^+);

HRMS found 369.1794, $C_{19}H_{26}N_2O_4Na$ requires 369.1790; Anal. Cald. For $C_{19}H_{26}N_2O_4$: C, 65.87, H, 7.56, N, 8.09. Found C, 65.61, H, 7.64, N, 7.79%.

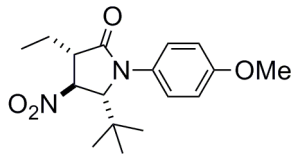
(3*S**, 4*S**, 5*R**)-3-Ethyl-5-*iso*propyl-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one (262)



262

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected *i*-propyl imine **332** (0.24 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **262**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **262** (0.12 g, 56%) as a white solid; mp. 116-118 °C; R_f 0.29 (20% Me_2CO/hexanes); IR υ_{max} 2966 (CH), 2937 (CH), 2878 (CH), 1702 (C=O), 1557 (NO_2), 1513, 1368, 1249 (C-O), 1033, 836 cm^{-1}; ^1H NMR (400 MHz) δ 0.78 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 0.96 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 1.12 (3H, t, *J* = 7.3, CH_2CH_3), 1.73 (1H, ddq, *J* = 14.2, 9.0, 7.4, C*H*$_2$CH$_3$), 2.04-2.18 (2H, m, C*H*$_2$CH$_3$ + C*H*(CH$_3$)$_2$), 3.15 (1H, ddd, *J* = 9.1, 6.3, 4.6, C*H*Et), 3.82 (3H, s, OC*H*$_3$), 4.56 (1H, dd, *J* = 5.1, 3.8, C*Hi*-Pr), 4.76 (1H, dd, *J* = 6.3, 5.1, *CH*NO_2), 6.93-6.96 (2H, m, Ar*H*), 7.22-7.27 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 11.1 (*C*H$_3$), 14.9 (*i*-Pr*C*H$_3$), 17.7 (*i*-Pr*C*H$_3$), 23.3 (*C*H$_2$), 27.7 (*i*-Pr*C*H), 49.9 (*C*HEt), 55.6 (O*C*H$_3$), 66.9 (*C*H*i*-Pr), 83.7 (*C*HNO_2), 114.2 (2 x Ar), 126.3 (2 x Ar), 128.8 (Cq), 158.4 (Cq), 170.9 (C=O); *m/z* (CI^+) 307 (100%, MH^+); HRMS found 307.1659, $C_{16}H_{23}N_2O_4$ requires 307.1658.

(3*S**, 4*S**, 5*R**)-5-*tert*-Butyl-3-ethyl-1-(4-methoxyphenyl)-4-nitropyrrolidin-2-one (264)

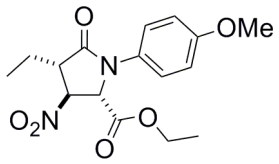


264

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected *t*-butyl imine **333** (0.26 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **264**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **264** (42 mg, 19%) as an orange oil; R_f 0.39

(20% Me_2CO/hexanes); IR υ_{max} 2964 (CH), 1701 (C=O), 1556 (NO_2) 1511, 1368, 1246 (C-O), 1032 cm^{-1}; ^1H NMR (400 MHz) δ 0.83 (9H, s, C(CH_3)$_3$), 1.16 (3H, t, *J* = 7.4, CH_2CH_3), 1.74 (1H, ddq, *J* = 14.4, 9.7, 7.4, CH_2CH_3), 2.15 (1H, dqd, *J* = 14.2, 7.6, 4.9, CH_2CH_3), 3.00 (1H app. dt, *J* = 9.8, 5.0, CHEt), 3.82 (3H, s, OCH_3), 4.47 (1H, d, *J* = 4.0, $CHC(CH_3)_3$), 4.80 (1H, dd, *J* = 5.2, 4.0, $CHNO_2$), 6.91-6.96 (2H, m, ArH), 7.20-7.27 (2H, m, ArH); ^{13}C NMR (125 MHz) δ 11.6 (CH_3), 23.6 (CH_2), 26.8 ($C(CH_3)_3$), 36.1 ($C(CH_3)_3$), 50.2 (CHEt), 55.6 (OCH_3), 71.9 ($CHC(CH_3)_3$), 85.8 ($CHNO_2$), 114.6 (2 x Ar), 127.5 (2 x Ar), 131.6 (Cq), 158.7 (Cq), 172.4 (C=O), *m/z* (ESI^+) 321 (55%, MH^+), 274 (100%, MH^+-NO_2); HRMS found 321.1808, $C_{17}H_{25}N_2O_4$ requires 321.1814.

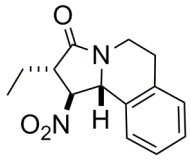
(2*S, 3*S**, 4*S**)-4-Ethyl-1-(4-methoxyphenyl)-3-nitro-5-oxopyrrolidin-2-carboxylic acid ethyl ester (265)**



265

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, PMP-protected ethyl ester imine **244** (0.29 g, 1.40 mmol) and TFA afforded crude pyrrolidinone **265**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **265** (0.16 g, 69%) as an orange oil; R_f 0.35 (20% Me_2CO/hexanes); IR υ_{max} 2970 (CH), 2938 (CH), 2839 (CH), 1743 (C=O), 1708 (C=O), 1555 (NO_2), 1511, 1369, 1245 (C-O), 1194, 1027 cm^{-1}; ^1H NMR (400 MHz) δ 1.14 (3H, t, *J* = 7.5, CH_2CH_3), 1.21 (3H, t, *J* = 7.3, OCH_2CH_3), 1.79 (1H, ddq, *J* = 14.7, 8.8, 7.3, CH_2CH_3), 2.11 (1H, dqd, *J* = 15.2, 7.6, 5.1, CH_2CH_3), 3.14 (1H, ddd, *J* = 9.2, 5.0, 4.3, CHEt), 3.73 (3H, s, OCH_3), 4.21 (2H, dq, *J* = 7.1, 1.9, OCH_2CH_3), 4.99 (1H, dd, *J* = 4.2, 3.4, $CHNO_2$), 5.21 (1H, d, *J* = 3.3, $CHCO_2Et$), 6.93 (2H, m, ArH), 7.33 (2H, m, ArH); ^{13}C NMR (125 MHz) δ 11.2 (CH_3), 14.0 (CH_3), 23.5 (CH_2), 49.5 (CHEt), 55.5 (OCH_3), 61.5 (CH_2), 62.9 ($CHCO_2Et$), 84.5 ($CHNO_2$), 114.5 (2 x Ar), 125.9 (2 x Ar), 129.2 (Cq), 158.6 (Cq), 168.5 (C=O), 171.3 (C=O); *m/z* (FAB^+) 359 (100%, MNa^+); HRMS found 359.1223, $C_{16}H_{20}N_2O_6Na$ requires 359.1219.

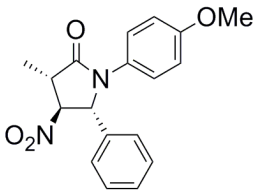
(1*S, 2*S**, 10b*R**)-2-Ethyl-1-nitro-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (269)**



269

Prepared by general procedure B: Nitroalkene **141** (0.10 g, 0.69 mmol), diethylzinc, imine **268** (0.18 g, 1.4 mmol) and TFA afforded crude pyrrolidinone **269**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidinone **269** (0.11 g, 60%) as a 5:1 mixture of diastereoisomers as a yellow oil; R_f 0.37 (20% Me_2CO/hexanes); diastereoisomer ratio calculated by C*H*NO_2 signal, δ major = 4.83, δ minor = 5.24. Major diastereoisomer; IR υ_{max} 2967 (CH), 2937 (CH), 2878 (CH), 1700 (C=O), 1552 (NO_2), 1459, 1428, 1367 cm^{-1}; ^{1}H NMR (600 MHz) δ (0.91 (3H, t, *J* = 7.2, CH_2CH_3), 1.68 (1H, app. dquint, *J* = 14.4, 7.2, CH_2CH_3), 1.94 (1H, dqd, *J* =14.4, 7.8, 4.8, CH_2CH_3), 2.77 (1H, dq, *J* = 16.2, 2.4, NCH_2CH_2), 2.92 (1H, ddd, *J* = 16.8, 11.4, 4.8, NCH_2CH_2), 3.14 (1H, dddd, *J* = 12.9, 10.2, 4.8, 1.8, NCH_2), 3.26 (1H, tdd, *J* = 8.4, 4.8, 1.2, C*H*Et), 4.34 (1H, ddd, *J* = 8.4, 6.0, 2.4, NCH_2), 4.81 (1H, dd, *J* = 8.4, 6.6, C*H*NO_2), 5.25, (1H, dd, *J* = 6.6, C*H*Ar), 7.12-7.17 (2H, m, Ar*H*), 7.25-7.29 (2H, m, Ar*H*); ^{13}C NMR (150 MHz) δ 10.3 (CH_3), 22.4 (CH_2), 28.3 (CH_2), 37.5 (CH_2), 49.8 (*C*HEt), 58.9 (*C*HAr), 90.5 (*C*HNO_2), 124.8 (Ar), 127.6 (Ar), 128.3 (Ar), 129.8 (Ar), 133.6 (Cq), 134.0 (Cq), 169.3 (C=O); *m/z* (CI^+) 261 (100%, MH^+); HRMS found 261.1238, $C_{14}H_{17}N_2O_3$, requires 261.1239; Minor diastereoisomer peaks: ^{1}H NMR (400 MHz) δ 1.10 (3H, t, *J* = 7.2, CH_2CH_3), 1.58-1.65 (1H, m, CH_2CH_3), 1.85-1.92 (1H, m, CH_2CH_3), 2.78 (1H, dd, *J* = 4.4, 2.4, CH_2Ar), 2.89-3.03 (1H, m, CH_2Ar), 3.13-3.22 (1H, m, NCH_2), 3.30 (1H, dddd, *J* = 12.8, 8.0, 4.8, 1.2, C*H*Et), 4.37 (1H, ddd, *J* = 13.2, 6.0, 2.4, NCH_2), 5.24 (1H, dd, *J* = 9.2, 6.0, C*H*NO_2), 5.47 (1H, d, *J* = 6.0, C*H*Ar), 7.11-7.20 (2H, m, Ar*H*), 7.26-7.33 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 11.7 (CH_3), 20.3 (CH_2), 28.1 (CH_2), 37.5 (CH_2), 47.3 (*C*HEt), 58.3 (*C*HAr), 88.5 (*C*HNO_2), 124.7 (Ar*C*H), 124.8 (Ar*C*H), 128.6 (Ar*C*H), 129.9 (Ar*C*H), 133.2 (Cq), 134.3 (Cq), 170.0 (C=O).

(3*S, 4*S**, 5*R**)-1-(4-Methoxyphenyl)-3-methyl-4-nitro-5-phenylpyrrolidin-2-one (270)**

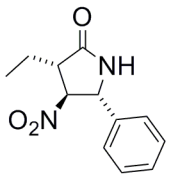


270

Prepared by general procedure B, except dimethylzinc was used. Nitroalkene **141** (0.10 g, 0.69 mmol), dimethylzinc, PMP-protected phenyl imine **227** (0.29 g, 1.4 mmol) and TFA afforded crude pyrrolidinone **270**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave **270** (0.14 g, 64%) as a white solid; mp. 114-116 °C; R_f 0.23 (20% Me_2CO/hexanes); IR υ_{max} 2938 (CH), 2837 (CH), 1702 (C=O), 1552 (NO_2), 1500, 1244 (C-O), 1031 cm^{-1}; ^1H NMR (400 MHz) δ 1.54 (3H, d, *J* = 7.3, CHC*H*$_3$), 3.38 (1H, quint, *J* = 7.3, C*H*CH_3), 3.73 (3H, s, OC*H*$_3$), 4.73 (1H, dd, *J* = 7.3, 5.8, C*H*NO_2), 5.63 (1H, d, *J* = 5.9, C*H*Ph), 6.77-6.81 (2H, m, Ar*H*), 7.22-7.37 (7H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 15.1 (*C*H_3), 42.6 (*C*HCH_3), 55.0 (O*C*H_3), 65.1 (*C*HPh), 92.4 (*C*HNO_2), 113.9 (2 x Ar), 124.6 (2 x Ar), 126.4 (2 x Ar), 128.8 (Ar), 129.0 (Cq), 129.1 (2 x Ar), 136.6 (Cq), 157.2 (Cq), 171.0 (C=O); *m/z* (ESI^+) 326 (100%, M^+); HRMS: found 326.1255, $C_{18}H_{18}N_2O_4$ requires 326.1261; Anal. Cald. For $C_{18}H_{18}N_2O_4$: C, 66.25, H, 5.56, N, 8.58. Found C, 66.07, H, 5.54, N, 8.38%.

5.4.3 Further Functionalisation

(3*S, 4*S**, 5*R**)- 3-Ethyl-4-nitro-5-phenyl-pyrrolidin-2-one (271)**

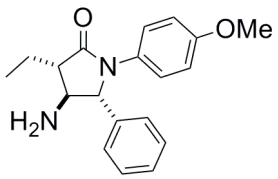


271

To a solution of **223** (0.10 g, 0.29 mmol) in MeCN (4 mL) at 0 °C under N_2 was added CAN (0.71 g, 1.2 mmol, 4.0 equiv.) as a solution in H_2O (4 mL) dropwise over 3 min. The solution immediately turned from pale yellow to dark orange. The mixture was stirred at 0 °C for a further 2 h over which time the solution became light

orange. To the mixture was added H_2O (30 mL) and the layers separated. The aq. layer was extracted with EtOAc (2 x 20 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford crude pyrrolidinone **271**. Purification by flash column chromatography (30% Me_2CO/hexanes) gave pyrrolidinone **271** (51 mg, 74%) as a yellow solid; mp. 87-89 °C; R_f 0.44 (30% Me_2CO/hexanes); IR υ_{max} 2968 (CH), 2926 (CH), 2878 (C-H), 1703 (C=O), 1552 (NO_2), 1457, 1367 cm^{-1}; ^1H NMR (400 MHz) δ 0.99 (3H, t, J = 7.4, CH_2CH_3), 1.71 (1H, app. dquint, J = 14.5, 7.5, CH_2CH_3), 1.96 (1H, dqd, J = 14.4, 7.5, 4.9, CH_2CH_3), 3.17 (1H, app. td, J = 7.7, 4.8, CHEt), 4.73 (1H, dd, J = 7.5, 6.0, $CHNO_2$), 5.16 (1H, d, J = 5.9, CHPh), 6.99 (1H, br s, NH), 7.31-7.33 (2H, m, ArH), 7.40-7.47 (3H, m, ArH); ^{13}C NMR (100 MHz) δ 10.2 (CH_3), 22.0 (CH_2), 44.3 (CHEt), 56.4 (CHPh), 91.8 ($CHNO_2$), 125.6 (3 x Ar), 128.8 (2 x Ar), 139.0 (Cq), 174.0 (C=O); *m/z* (FAB$^+$) 257 (45%, MNa^+), 235 (30%, MH^+); HRMS: found 257.0905, $C_{12}H_{14}N_2O_3Na$ requires 257.0902; Anal. Cald. For $C_{12}H_{14}N_2O_3$: C, 61.53, H, 6.02, N, 11.96. Found C, 61.12, H, 5.99, N 11.86%.

(3*S, 4*S**, 5*R**)-4-Amino-3-ethyl-1-(4-methoxyphenyl)-5-phenylpyrrolidin-2-one (272)**

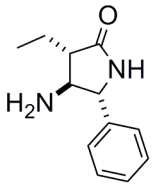


272

To a solution of pyrrolidinone **223** (100 mg, 290 μmol) in EtOAc/MeOH (2:1, 6 mL) at 0 °C under N_2 was added 6 M HCl (1.47 mL, 8.82 mmol, 30.0 equiv.). To the mixture was added zinc dust (1.15 g, 0.04 g.atom, 60.0 equiv.) portionwise over 20 min. The mixture was then warmed to rt and stirred for a further 15 h before sat. aq. $NaHCO_3$ (30 mL) was added. The pH of the aq. layer was tested and additional sat. aq. $NaHCO_3$ was added as necessary to reach pH 9. To the mixture was added EtOAc (20 mL) and the layers separated. The aq. layer was extracted with EtOAc (2 x 20 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*, to give amine **272** as an off white solid (83.0 mg, 91%); mp. 174-172 °C; R_f 0.22 (20% Me_2CO/hexanes); IR υ_{max} 2961 (CH), 2932 (CH), 2876 (CH), 1689 (C=O), 1510, 1456, 1370, 1246 (C-O), 1031

cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (3H, t, *J* = 7.4, CH_2CH_3), 1.72 (2H, br s, NH_2), 1.82 (1H, app. dquint, *J* = 14.5, 7.3, CH_2CH_3), 1.97 (1H, dqd, *J* = 14.9, 7.4, 5.2, CH_2CH_3), 2.43 (1H, ddd, *J* = 11.8, 6.7, 5.3, C*H*Et), 3.20 (1H, dd, *J* = 9.2, 7.1, C*H*NH_2), 3.70 (3H, s, OCH_3), 4.66 (1H, d, *J* = 7.0, C*H*Ar), 6.71-6.75 (2H, m, Ar*H*), 7.15-7.19 (2H, m, Ar*H*), 7.20-7.24 (3H, m, Ar*H*), 7.26-7.31 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 11.2 (CH_3), 22.2 (CH_2), 51.8 (*C*HEt), 55.3 (OCH_3), 60.9 (*C*HNH_2), 71.3 (*C*HAr), 113.9 (2 x Ar), 124.9 (2 x Ar), 127.1 (2 x Ar), 128.1 (Ar), 128.9 (2 x Ar), 130.6 (Cq), 139.0 (Cq), 156.9 (Cq), 174.5 (C=O); *m/z* (FAB^+) 333 (20%, MNa^+); HRMS found 333.1567, $C_{19}H_{22}N_2O_2Na$ requires 333.1579.

(3*S, 4*S**, 5*R**)-4-Amino-3-ethyl-5-phenylpyrrolidin-2-one (273)**

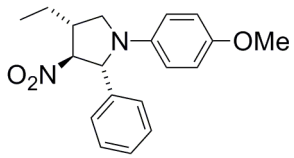


273

To a solution of pyrrolidinone **272** (37 mg, 0.16 mmol) in EtOAc/MeOH (2:1, 6 mL) at 0 °C under N_2 was added 6 M HCl (0.79 mL, 4.7 mmol, 30.0 equiv.). To the mixture was added zinc dust (1.2 g, 0.04 g.atom, 60.0 equiv.) portionwise over 20 min. The mixture was then warmed to rt and stirred for a further 15 h. Sat. aq. $NaHCO_3$ (30 mL) was added carefully, followed by EtOAc (20 mL) and the layers were separated. The pH of the aq. layer was tested and additional sat. aq. $NaHCO_3$ was added as necessary to reach pH 9. The aq. layer was extracted with EtOAc (2 x 20 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give amine **273** as an off white solid (16 mg, 49%); mp. 149-151 °C; R_f 0.27 (50% Me_2CO/hexanes); IR υ_{max} 3230 (NH_2), 2963 (CH), 2927 (CH), 2876 (CH), 1689 (C=O), 1630, 1456, 1278 cm^{-1}; ^1H NMR (400 MHz) δ 1.05 (3H, t, *J* = 7.5, CH_2CH_3), 1.71 (1H, ddq, *J* = 14.4, 7.6, 7.4, CH_2CH_3), 1.84 (1H, ddq, *J* = 14.2, 7.5, 5.4, CH_2CH_3), 2.06 (2H, br s, NH_2), 2.30 (1H, ddd, *J* = 9.3, 6.3, 5.5, C*H*Et), 3.15 (1H, app. t, *J* = 8.6, C*H*NH_2), 4.24 (1H, d, *J* = 7.2, C*H*Ph), 6.03 (1H, br s, N*H*), 7.32-7.42 (5H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 11.0 (CH_3), 22.2 (CH_2), 51.8 (*C*HEt), 62.2 (*C*HNH_2), 65.5 (*C*HPh), 127.6 (2 x Ar), 129.4 (Ar), 129.9 (2 x Ar), 141.5 (Cq), 179.2

(C=O); *m/z* (CI^+) 205 (100%, MH^+); HRMS found 205.1338, $C_{12}H_{17}N_2O$ requires 205.1341.

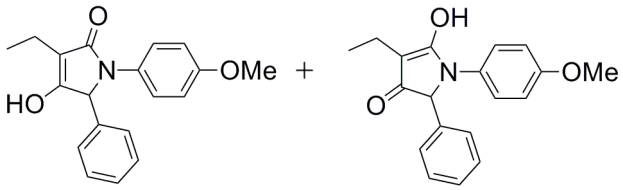
(2*R, 3*S**, 4*R**)-4-Ethyl-1-(4-methoxyphenyl)-3-nitro-2-phenyl-pyrrolidine (274)**



274

To a solution of pyrrolidinone **223** (70 mg, 0.21 mmol) in THF (5 mL) under N_2 at 0 °C was added BH_3-THF complex (0.72 mL of a 1.0 M sol. in THF, 0.72 mmol, 3.5 equiv.) dropwise over 2 min. The mixture was stirred at 0 °C until no more effervescence was observed before being heated to reflux for 15 h. The mixture was cooled to rt and MeOH (20 mL) was added before being concentrated *in vacuo* to give crude pyrrolidine **274**. Purification by flash column chromatography (20% Me_2CO/hexanes) gave pyrrolidine **274** (53 mg, 79%) as a yellow solid; mp. 50-52 °C; R_f 0.21 (20% Me_2CO/hexanes); IR υ_{max} 2964 (CH), 2932 (CH), 1548 (NO_2), 1510, 1358, 1241 (C-O), 1180, 1038 cm^{-1}; ^1H NMR (400 MHz) δ 0.97 (3H, t, *J* = 7.4, CH_2CH_3), 1.58 (2H, app. dquint, *J* = 7.4, 2.6, CH_2CH_3), 2.85 (1H, m, C*H*Et), 3.67 (1H, dd, *J* = 9.2, 5.6, NCH_2), 3.72 (3H, s, OCH_3), 3.85 (1H, dd, *J* = 9.2, 8.0, NCH_2), 4.76 (1H, app. t, *J* = 5.3, C*H*NO_2), 5.13 (1H, d, *J* = 4.8, C*H*Ph), 6.46-6.50 (2H, m, Ar*H*), 6.74-6.78 (2H, m, Ar*H*), 7.28-7.34 (5H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 12.1 (CH_3), 25.6 (CH_2), 45.2 (*C*HEt), 54.9 (NCH_2), 55.7 (OCH_3), 68.5 (*C*HPh), 97.8 (*C*HNO_2), 114.7 (2 x Ar), 114.9 (2 x Ar), 126.1 (2 x Ar), 128.2 (Ar), 129.2 (2 x Ar), 140.0 (Cq), 141.1 (Cq), 152.2 (Cq); *m/z* (ESI^+) 326 (54%, M^+), 250 (100%, MH^+-Ph); HRMS: found 326.1626, $C_{19}H_{22}N_2O_3$ requires 326.1625; Anal. Cald. For $C_{19}H_{22}N_2O_3$: C, 69.92, H, 6.79, N, 8.58. Found C, 70.20, H, 6.86, N, 8.54%.

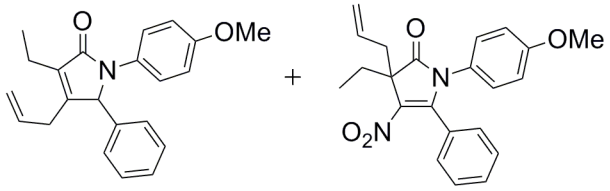
3-Ethyl-4-hydroxy-1-(4-methoxyphenyl)-5-phenyl-1,5-dihydro-pyrrol-2-one (275) and 3-Ethyl-4-hydroxy-1-(4-methoxyphenyl)-5-phenyl-3,4-dihydro-pyrrol-3-one (276)



275 **276**

To a solution of potassium dichromate (260 mg, 880 μmol, 6.0 equiv.) in 6 M HCl (6.40 mL, 26.4 mmol, 180.0 equiv.) at 0 °C under N_2 was added zinc dust (0.48 g, 0.02 g.atom, 50.0 equiv.) portionwise over 20 min. During the addition the solution changed from orange to dark blue. After complete dissolution of the zinc, the resulting $CrCl_2$ solution was transferred to a refluxing solution of pyrrolidinone **223** (50 mg, 0.15 mmol) in MeOH:EtOAc (2.5:1, 7 mL). The solution was refluxed for 1 h before being cooled to rt and sat. aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL) were added and the layers separated. The aq. layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude pyrrolones **275** and **276**. Purification by flash column chromatography (30% Me_2CO/hexanes) gave pyrrolones **275** and **276** as an inseparable 1:1 mixture of tautomers (18 mg, 39%) as a yellow oil; R_f 0.09 (20% Me_2CO/hexanes); IR υ_{max} 3367 (OH), 2971 (CH), 2937 (CH), 2839 (CH), 1776 (C=O), 1689 (C=O), 1512, 1250 (C-O), 1031 cm^{-1}; ^1H NMR (600 MHz) δ 0.93 (3H, t, *J* = 7.5, CH_2CH_3), 1.07 (3H, t, *J* = 7.5, CH_2CH_3), 1.77 (1H, app. quint, *J* = 7.2, CH_2CH_3), 1.96 (1H, tq, *J* = 14.8, 7.5, CH_2CH_3), 2.05-2.11 (2H, tq, *J* = 14.8, 7.5, CH_2CH_3), 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 5.39 (1H, s, CHPh), 5.52 (1H, s, CHPh), 6.80-6.82 (2H, m, ArH), 6.84-6.86 (2H, m, ArH), 7.22-7.23 (2H, m, ArH), 7.29-7.35 (10H, m, ArH), 7.48-7.49 (2H, m, ArH); ^{13}C NMR (125 MHz) δ 6.9 (CH_3), 7.4 (CH_3), 30.1 (CH_2), 30.6 (CH_2), 55.5 (2 x OCH_3), 69.2 (CHPh), 70.3 (CHPh), 75.7 (Cq), 75.9 (Cq), 114.3 (2 x Ar), 114.5 (2 x Ar), 123.4 (2 x Ar), 125.2 (2 x Ar), 126.2 (2 x Ar), 128.0 (2 x Ar), 128.9 (2 x Ar), 128.9 (Cq), 129.2 (2 x Ar), 129.3 (2 x Ar), 129.7 (Cq), 132.6 (Cq), 133.6 (Cq), 157.5 (Cq), 157.9 (Cq), 171.7 (C=O), 172.1 (C=O), 203.6 (Cq), 205.5 (Cq); *m/z* (ESI^+) 309 (20%, M^+); HRMS: found 309.1368, $C_{19}H_{19}NO_3$ requires 309.1368.

4-Allyl-3-ethyl-1-(4-methoxyphenyl)-5-phenyl-1-5-dihydro-pyrrol-2-one (280) and 3-allyl-3-ethyl-1-(4-methoxyphenyl)-4-nitro-5-phenyl-1,3-dihydro-pyrrol-2-one (278)

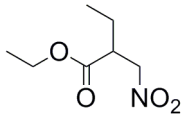


280 **278**

To a solution of *i*-Pr_2NH (29 μL, 0.21 mmol, 1.05 equiv.) in THF (5 mL) at 0 °C under N_2, was added *n*-butyllithium (82 μL, of a 2.5 M sol. in THF, 0.21 mmol, 1.05 equiv.) dropwise. The mixture was warmed to rt and stirred for 15 min before being cooled to –78 °C and pyrrolidinone **223** (70 mg, 0.20 mmol) in THF (2 mL) added *via* cannula. The mixture was stirred for 30 min before allyl bromide (24 μL, 0.20 mmol, 1.0 equiv.) was added *via* cannula. The mixture was then warmed to rt and stirred for a further 2 h before sat. aq. NH_4Cl (10 mL) and Et_2O (20 mL) were added and the layers separated. The aq. layer was extracted with Et_2O (2 x 10 mL) and the combined organics washed with 1 M HCl (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude pyrrolones **280** and **278**. Purification by flash column chromatography gave in order of elution pyrrolone **280** (2.4 mg, 4%) as a yellow oil; R_f 0.50 (20% Me_2CO/hexanes); IR υ_{max} 2928 (CH), 1720 (C=O), 1512, 1446, 1370, 1292, 1249 (C-O), 1168 cm^{-1}; ^1H NMR (400 MHz) δ 0.91 (3H, t, *J* = 7.2, CH_2CH_3), 1.74 (1H, dq, *J* = 15.2, 7.6, CH_2CH_3), 1.87 (1H, dq, *J* = 14.8, 7.6, CH_2CH_3), 2.44-2.55 (2H, m, $CH_2CH{=}CH_2$), 3.77 (3H, s, OCH_3), 5.06 (1H, app. dt, *J* = 10.0, 1.0, $CH{=}CH_2$), 5.16 (1H, dd, *J* = 17.2, 2.0, $CH{=}CH_2$), 5.42 (1H, s, CHPh), 5.77 (1H, ddt, *J* = 16.8, 10.0, 7.4, $CH{=}CH_2$), 6.78-6.82 (2H, m, Ar*H*), 6.92-6.96 (2H, m, Ar*H*), 7.12-7.15 (2H, m, Ar*H*), 7.20-7.26 (3H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 9.1 (CH_3), 29.5 (CH_3CH_2), 41.3 ($CH_2CH{=}CH_2$), 55.2 (OCH_3), 55.4 (Cq), 111.7 (CHPh), 114.0 (2 x Ar), 118.3 ($CH_2CH{=}CH_2$), 127.8 (2 x Ar), 128.2 (2 x Ar), 128.3 (2 x Ar), 128.5 (Ar), 128.7 (Cq), 131.4 (Cq), 133.4 ($CH_2{=}CH$), 144.5 (Cq), 158.3 (Cq), 181.8 (C=O); *m/z* (CI^+) 334 (100%, MH^+); HRMS: found 334.1799, $C_{22}H_{24}NO_2$ requires 334.1807; and pyrrolone **278** (18.5 mg, 24%) as a yellow oil; R_f 0.36 (20% Me_2CO/hexanes); IR υ_{max} 2967 (CH), 1744 (C=O), 1513, 1333, 1251 (C-O), 1142 cm^{-1}; ^1H NMR (400 MHz) δ 0.95 (3H, t, *J* = 7.6, CH_2CH_3), 2.04 (1H, dq, *J*

= 13.6, 7.2, C*H*$_2$CH$_3$), 2.36 (1H, dq, *J* = 13.6, 7.2, C*H*$_2$CH$_3$), 2.69 (1H, dd, *J* = 16.0, 1.6, C*H*$_2$CH=CH$_2$), 3.07 (1H, dd, *J* = 12.8, 7.6, C*H*$_2$CH=CH$_2$), 3.74 (3H, s, OC*H*$_3$), 5.16 (1H, dd, *J* = 8.4, 2.0, CH=C*H*$_2$), 5.21 (1H, dd, *J* = 16.0, 1.6, CH=C*H*$_2$), 5.75 (1H, app. ddt, *J* = 17.2, 10.0, 7.6, C*H*=CH$_2$), 6.73-6.76 (2H, m, Ar*H*), 6.81-6.83 (2H, m, Ar*H*), 7.16-7.18 (2H, m, Ar*H*), 7.29-7.39 (3H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 9.3 (*C*H$_3$), 29.0 (*C*H$_2$), 40.6 (*C*H$_2$CH=CH$_2$), 55.5 (O*C*H$_3$), 56.4 (Cq), 114.1 (2 x Ar), 119.9 (*C*H$_2$=CH), 123.3 (Ar), 125.5 (Ar), 126.9 (Ar), 127.7 (Cq), 128.4 (2 x Ar), 129.1 (2 x Ar), 130.4 (*C*H=CH$_2$), 131.7 (Ar*C*H), 154.2 (Cq), 159.5 (Cq), 177.9 (C=O); *m/z* (ESI$^+$) 379 (100%, MH$^+$); HRMS: found 379.1647, $C_{22}H_{23}N_2O_4$ requires 379.1658.

2-Nitromethyl-butyric acid ethyl ester (320)

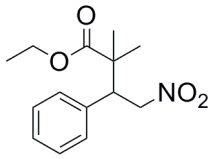


320

To a solution of nitroalkene **141** (0.10 g, 0.69 mmol) in THF (3 mL) under N_2 was added Cu(OTf)$_2$ (12.4 mg, 34.0 μmol, 5 mol%). The mixture was cooled to -78 °C and diethylzinc (0.76 mL of a 1.0 M sol. in hexanes, 0.76 mmol, 1.1 equiv.) was added dropwise. The now orange mixture was stirred at this temperature for 10 min before being warmed to rt and stirred for a further 1.5 h. The mixture was re-cooled to –78 °C and benzaldehyde (146 mg, 1.38 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min before TFA (58.0 μL, 0.69 mmol, 1.0 equiv.) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being heated at reflux for 16 h. The mixture was cooled and sat. aq. NaHCO$_3$ (20 mL) and Et$_2$O (20 mL) were added and the layers separated. The aq. layer was extracted with Et$_2$O (3 x 20 mL) and the combined organics washed with brine (20 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give crude 1,4-addition product **320**. Purification by flash column chromatography (20% Me$_2$CO/hexanes) gave **320** (81 mg, 67%) as a colourless oil; R$_f$ 0.27 (20% Me$_2$CO/hexanes); IR υ_{max} 2975 (CH), 2941 (CH), 2882 (CH), 1729 (C=O), 1555 (NO$_2$), 1379, 1190 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.97 (3H, t, *J* = 7.5, CH$_2$C*H*$_3$), 1.27 (3H, t, *J* = 7.1, OCH$_2$C*H*$_3$), 1.69 (2H, app. dquint, *J* = 14.4, 7.2, C*H*$_2$CH$_3$), 3.13 (1H, dtd, *J* = 9.6, 9.2, 4.8, C*H*Et), 4.19 (2H, q, *J* = 7.2, OC*H*$_2$CH$_3$), 4.42 (1H, dd, *J* = 14.3, 4.9, C*H*$_2$NO$_2$), 4.73 (1H, dd, *J* = 14.3, 9.2,

C*H*$_2$NO$_2$); ^{13}C NMR (125 MHz) δ 11.1 (*C*H$_3$), 14.2 (*C*H$_3$), 22.6 (*C*H$_2$), 44.3 (*C*H), 61.4 (O*C*H$_2$), 75.0 (*C*H$_2$), 172.2 (C=O); *m/z* (CI$^+$) 176 (100%, MH$^+$), 130 (50%, MH$^+$-NO$_2$); HRMS: found 176.0926, $C_7H_{14}NO_4$ requires 176.0923.

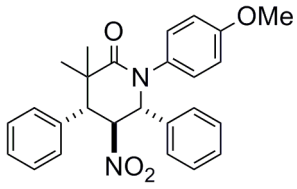
2,2-Dimethyl-4-nitro-3-phenylbutyric acid ethyl ester (307)



307

To a solution of *i*-Pr$_2$NH (0.20 mL, 0.14 mmol, 1.2 equiv.) in THF (5 mL) at 0 °C under N$_2$ was added *n*-butyllithium (0.56 mL, of a 2.5 M sol. in THF, 0.14 mmol, 1.2 equiv.) dropwise over 5 min. The solution was then warmed to rt for 15 min before being cooled to –78 °C. To the mixture was added ethyl isobutyrate (0.19 mL, 0.14 mmol, 1.2 equiv.) dropwise and the reaction mixture stirred for 1 h before β-nitrostyrene (0.18 g, 1.2 mmol, 1.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for a further 1 h before being warmed to rt for 2 h. To the mixture was added 1 M HCl (20 mL) and Et$_2$O (20 mL) and the layers separated. The aq. layer was extracted with Et$_2$O (2 x 20 mL) and the combined organics washed with brine (20 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give crude **307**. Purification by flash column chromatography (20% Me$_2$CO/hexanes) gave **307** (0.17 g, 53%) as a colourless oil; R$_f$ 0.47 (20% Me$_2$CO/hexanes); IR υ_{max} 2982 (CH), 1719 (C=O), 1552 (NO$_2$), 1456, 1379, 1249 (C-O), 1130 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.17 (3H, s, C(C*H*$_3$)$_2$), 1.20 (3H, s, C(C*H*$_3$)$_2$), 1.27 (3H, t, *J* = 7.2, OCH$_2$C*H*$_3$), 3.80 (1H, dd, *J* = 11.2, 4.0, C*H*Ph), 4.16 (2H, m, OC*H*$_2$CH$_3$), 4.78 (1H, dd, *J* = 13.2, 4.0, C*H*$_2$NO$_2$), 4.97 (1H, dd, *J* = 13.2, 11.6, C*H*$_2$NO$_2$), 7.17-7.21 (2H, m, Ar*H*), 7.26-7.36 (3H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 14.2 (OCH$_2$*C*H$_3$), 22.3 (C*C*H$_3$), 25.2 (C*C*H$_3$), 45.4 (Cq), 51.4 (*C*HPh), 61.2 (O*C*H$_2$CH$_3$), 77.3 (*C*H$_2$NO$_2$), 128.3 (Ar), 128.5 (2 x Ar), 129.4 (2 x Ar), 136.1 (Cq), 176.0 (C=O); *m/z* (FAB$^+$) 288 (100%, MNa$^+$), 266 (50%, MH$^+$); HRMS: found 288.1209, $C_{14}H_{19}NO_4Na$ requires 288.1212.

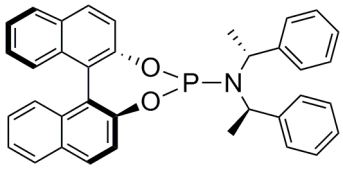
1-(4-Methoxyphenyl)-3,3,-dimethyl-5-nitro-4,6-diphenyl-piperidin-2-one (308)



308

To a solution of *i*-Pr_2NH (2.27 mL, 1.61 mmol, 1.2 equiv.) in THF (5 mL) at 0 °C under N_2 was added *n*-butyllithium (640 μL of a 2.5 M sol. in hexanes, 1.61 mmol, 1.2 equiv.) dropwise over 2 min. The mixture was warmed to rt and stirred for 15 min before being cooled to –78 °C and ethyl isobutyrate **306** (220 μL, 1.61 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred for 1 h before nitrostyrene (200 mg, 1.34 mmol) in THF (3 mL) was added *via* cannula. The mixture was stirred for a further 10 min at –78 °C before being warmed to rt for 2 h. The mixture was re-cooled to –78 °C and PMP-protected phenyl imine **227** (570 mg, 2.68 mmol, 2.0 equiv.) was added *via* cannula. The mixture was stirred for a further 20 min before TFA (360 μL, 4.70 mmol, 3.5 equiv.) in THF (2 mL) was added *via* cannula fast dropwise. The mixture was stirred at –78 °C for a further 1 h before being warmed to rt and stirred for 15 h. Sat. aq. $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aq. layer was extracted with Et_2O (2 x 20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude piperidinone **308**. Purification by flash column chromatography (10-30% Me_2CO/hexanes) gave piperidinone **308** (40.0 mg, 7%) as a yellow oil; R_f 0.08 (10% Me_2CO/hexanes); IR υ_{max} 2973 (CH), 2935 (CH), 1659 (C=O), 1558 (NO_2), 1511, 1458, 1389, 1298, 1249 (C-O) cm^{-1}; ^1H NMR (400 MHz) δ 1.25 (3H, s, CC*H*$_3$), 1.45 (3H, s, CC*H*$_3$), 3.71 (3H, s, OC*H*$_3$), 3.90 (1H, d, *J* = 12.8, PhC*H*C$(CH_3)_2$), 5.36 (1H, d, *J* = 9.6, C*H*NO_2), 5.63 (1H, dd, *J* = 12.4, 9.6, PhC*H*NAr), 6.72-6.74 (2H, m, Ar*H*), 6.98-7.00 (2H, m, Ar*H*), 7.15-7.17 (2H, m, Ar*H*), 7.23-7.29 (6H, m, Ar*H*), 7.32-7.35 (2H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 23.0 (C$(CH_3)_2$), 25.9 (C$(CH_3)_2$), 43.0 (Cq), 52.6 (*C*HPh), 55.4 (OCH_3), 67.7 (*C*HPh), 90.5 (*C*HNO_2), 114.2 (2 x Ar), 127.7 (2 x Ar), 128.5 (6 x Ar), 129.2 (4 x Ar), 132.9 (Cq), 133.7 (Cq), 136.6 (Cq), 158.2 (Cq), 175.3 (C=O); *m/z* (ESI^+) 431 (35%, MH^+), 384 (100%, M^+-NO_2); HRMS: found 431.1962, $C_{26}H_{27}N_2O_4$ requires 431.1971.

***O,O'-(S)*-1,1'-Dinapthyl-2,2'-diyl-*N-N*-di-*(R,R)*-1-(phenyl)-ethylphosphoramidite (299)[125]**



299

To a solution of (+)-bis[(*R*)-1-phenylethyl]amine-hydrochloride (1.0 g, 3.8 mmol) in CH_2Cl_2 (40 mL) at rt under N_2 was added Et_3N (0.53 mL, 3.8 mmol) and the mixture stirred for 1 h. To the solution was added H_2O (50 mL) and CH_2Cl_2 (50 mL) and the layers separated. The aq. layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude chiral amine **298** (0.75 g, 86%). To a solution of crude amine **298** (0.75 g, 3.3 mmol) and Et_3N (0.51 mL, 3.7 mmol, 1.1 equiv.) in toluene (20 mL) at rt was added a solution of PCl_3 (0.29 mL, 3.3 mmol, 1.0 equiv.) in toluene (50 mL) dropwise over 30 min. The mixture was then heated at 75 °C for 6 h before being cooled to rt and Et_3N (1.0 mL, 7.3 mmol, 2.2 equiv.) was added. The mixture was cooled to –78 °C and a solution of (*S*)-(-)-1,1'-bi(2-napthol) **297** (0.96 g, 3.3 mmol) in toluene:THF (6:1, 28 mL) was added over 30 min. The mixture was then stirred for 1 h before being warmed to rt and stirred for a further 15 h. The mixture was filtered and concentrated *in vacuo* to give crude phosphoramidite **299**. Purification by flash column chromatography (20% CH_2Cl_2/hexanes) gave phosphoramidite **299** (0.41 g, 23%, lit.[125] 20%) as a white solid; mp. 99-101 °C; R_f 0.19 (20% CH_2Cl_2/hexanes); $[\alpha]_D$ +401.7 (c 0.64, $CHCl_3$), [lit.[125] $[\alpha]_D$ +411.1 (c 0.99, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ 1.76 (6H, d, *J* = 7.1, 2 x CHC*H*$_3$), 4.53 (2H, dq, *J* = 11.6, 6.8, 2 x C*H*CH$_3$), 7.19-7.21 (10H, m, Ar*H*), 7.23-7.28 (2H, m, Ar*H*), 7.31 (1H, d, *J* = 8.0, Ar*H*), 7.39-7.44 (4H, m, Ar*H*), 7.45 (1H, dd, *J* = 8.0, 0.8, Ar*H*), 7.90 (2H, ddd, *J* = 8.4, 4.8, 1.2, Ar*H*), 7.96 (2H, d, *J* = 8.8, Ar*H*). Data in agreement with that reported.[125]

6.0 Appendix 1 – Table of Coupling Constants

The following table contains observed coupling constants for the pyrrolidinones synthesised during these studies. The notation J_{1A} refers to the coupling observed between proton H_A and H_B in the proton signal for H_A and notation J_{1B} refers to the same coupling, but that observed in the signal for proton H_B. The coupling constants have not been averaged and are quoted as observed in the ^{1}H NMR spectra (Figure 6.0).

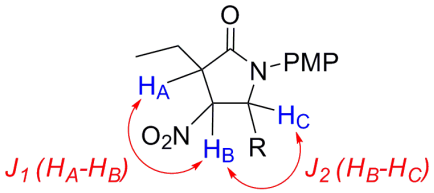
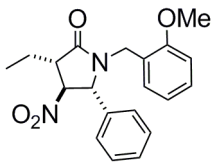
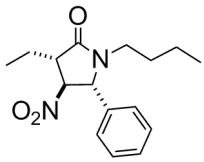
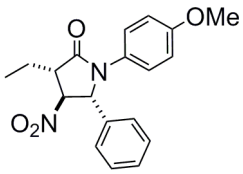
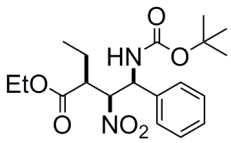
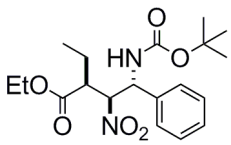
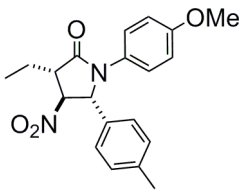
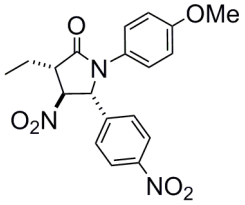
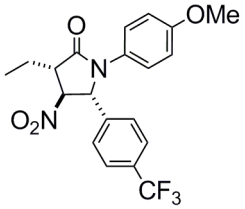
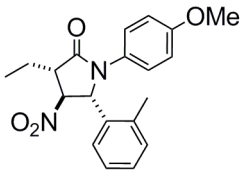
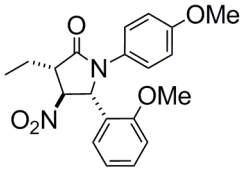
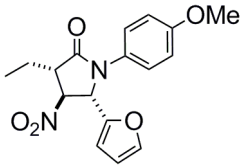
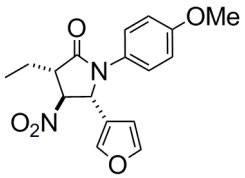
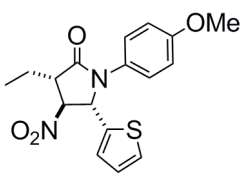
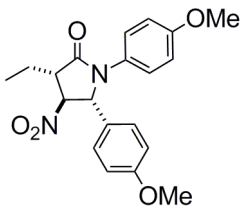
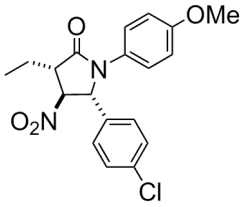
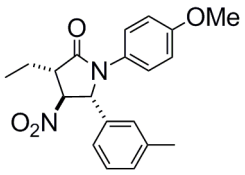
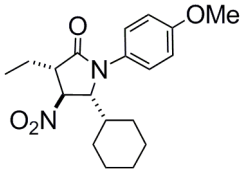
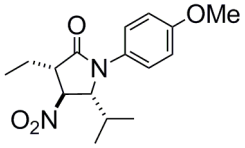
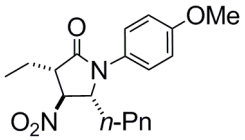
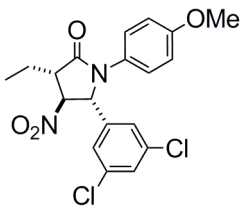
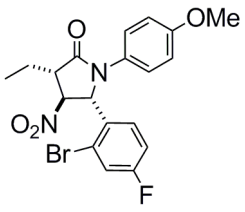


Figure 6.0: Protons referring to coupling constants in the ^{1}H NMR spectra.

Entry	**Structure**	J_{1A}	J_{1B}	J_{2B}	J_{2C}
1		6.7	6.6	5.3	5.3
2		6.8	6.8	5.4	5.4
3		6.8	6.8	5.2	5.3
4		9.6	9.5	9.5	9.4
5		11.3	11.0	3.8	3.6

6		6.8	6.8	5.3	5.3
7		7.8	7.1	5.7	5.7
8		7.6	6.6	5.5	5.7
9		5.2	5.3	4.3	4.2
10		4.9	4.4	4.4	4.0
11		5.9	5.9	4.9	4.7
12		7.6	7.0	5.6	5.5
13		6.8	6.4	5.4	5.1

14		7.1	7.0	5.5	5.4
15		7.1	7.0	5.5	5.5
16		6.8	6.8	5.4	5.4
17		4.8	4.2	4.2	5.4
18		6.3	6.3	5.1	5.1
19		6.0	5.9	5.2	4.5
20		7.0	7.0	5.4	5.5
21		6.8	6.3	6.3	5.5

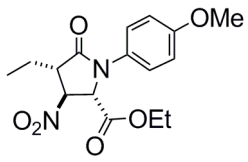
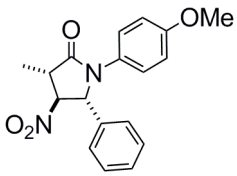
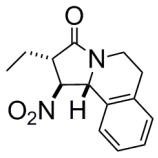
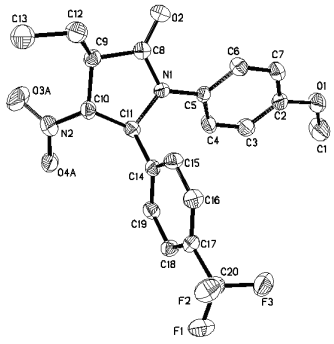
22		4.3	4.2	3.4	3.3
23		7.3	7.3	5.8	5.9
24		8.4	8.4	6.6	6.6

Table 6.0: Coupling constants for synthesised pyrrolidinones.

6.1 Appendix 2 – Crystallographic Data



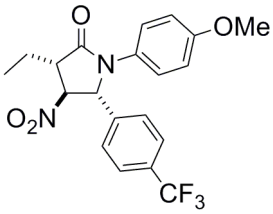
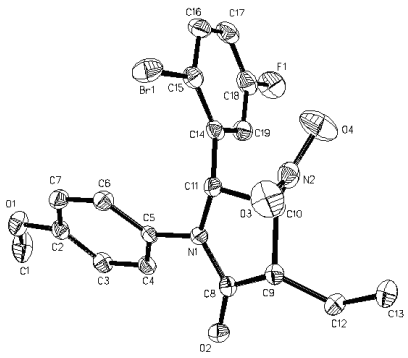


Table 1. Crystal data and structure refinement for str0811.

Identification code	str0811	
Chemical formula	$C_{20}H_{19}F_3N_2O_4$	
Formula weight	408.37	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	a = 13.739(3) Å	α = 90°
	b = 8.094(2) Å	β = 105.856(6)°
	c = 17.500(4) Å	γ = 90°
Cell volume	1872.1(8) $Å^3$	
Z	4	
Calculated density	1.449 g/cm^3	
Absorption coefficient μ	0.121 mm^{-1}	
F(000)	848	
Crystal colour and size	colourless, 0.48 × 0.44 × 0.36 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.20 to 28.13°	
Index ranges	h –11 to 15, k –10 to 9, l –9 to 21	
Completeness to θ = 26.00°	71.3 %	
Reflections collected	4967	
Independent reflections	2958 (R_{int} = 0.0187)	
Reflections with $F^2>2\sigma$	2429	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.9443 and 0.9578	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0805, 0.7257	
Data / restraints / parameters	2958 / 0 / 281	
Final R indices [$F^2>2\sigma$]	R1 = 0.0449, wR2 = 0.1243	
R indices (all data)	R1 = 0.0559, wR2 = 0.1456	
Goodness-of-fit on F^2	1.047	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.200 and –0.274 e $Å^{-3}$	

6.2 Appendix 3 - Crystallographic Data



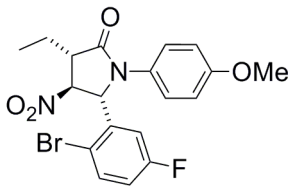


Table 1. Crystal data and structure refinement for str0816.

Identification code	str0816	
Chemical formula	$C_{19}H_{18}BrFN_2O_4$	
Formula weight	437.26	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/n$	
Unit cell parameters	a = 6.9144(11) Å	α = 90°
	b = 13.544(2) Å	β = 94.424(3)°
	c = 19.373(3) Å	γ = 90°
Cell volume	1808.9(5) $Å^3$	
Z	4	
Calculated density	1.606 g/cm^3	
Absorption coefficient μ	2.311 mm^{-1}	
F(000)	888	
Crystal colour and size	colourless, 0.46 × 0.10 × 0.06 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.59 to 28.30°	
Index ranges	h –9 to 9, k –17 to 17, l –25 to 24	
Completeness to θ = 26.00°	99.2 %	
Reflections collected	14727	
Independent reflections	4231 (R_{int} = 0.0408)	
Reflections with $F^2>2\sigma$	3290	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.4162 and 0.8738	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0732, 0.1890	
Data / restraints / parameters	4231 / 0 / 244	
Final R indices [$F^2>2\sigma$]	R1 = 0.0419, wR2 = 0.1076	
R indices (all data)	R1 = 0.0582, wR2 = 0.1183	
Goodness-of-fit on F^2	0.980	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.915 and –0.632 e $Å^{-3}$	

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Part 2: Towards the Synthesis of Popolohuanone E

1.0 Introduction

Originally defined as the chemistry of substances produced by living organisms, organic chemistry has now extended to the study of carbon containing compounds, their structure, properties and the synthesis of artificial substances. As organic chemistry has developed and more natural products have been isolated, increasingly complex structures have been successfully synthesised. This plays a vital role in medicinal and biological chemistry and the development of active pharmaceutical compounds depends on our ability to isolate, recreate and modify these compounds.

1.1 Popolohuanone E

Popolohuanone E (**1**) is a marine natural product isolated from the Pohnpei Sponge *Dysidea* sp.[1] The isolation method and structure of **1** was published by Scheuer *et al.* in 1993 and there has been no total synthesis to date. The intricate structure contains a unique trihydroxylated dibenzofuran-1,4-dione central core as well as two identical sesquiterpene units, each of which contain four contiguous stereocentres. The complex architecture and interesting biological activity of **1** has made this natural product a particularly desirable target for synthesis (Figure 1.0).

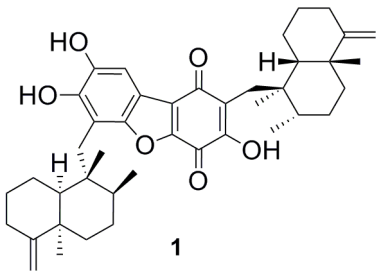


Figure 1.0: Popolohuanone E (**1**).

The freeze dried *Dysidea* sponge (39 g) was collected from the Federal States of Micronesia and extracted with 200 mL of 2-propanol/CH_2Cl_2 (1:1) to afford 377 mg of dark purple residue. This residue was then partitioned between 200 mL of hexanes/MeOH (2:1) and the upper layer residue (148.6 mg) was subjected to C-18 flash chromatography. The fraction eluting with 100% MeOH (23.5 mg) was repeatedly chromatographed to yield 15.6 mg of **1** as a dark purple solid.

Fractions eluting from the C-18 column prior to **1** contained the known arenarol (**2**)[2] and several other arenarol derivatives. Mass spectrometry and NMR data suggested

that **1** was a dimerised arenarol derivative reminiscent of popolohuanone A (**3**)[3] but containing an additional ring to give a trihydroxy dibenzofuran-1,4-dione central core (Figure 1.1).

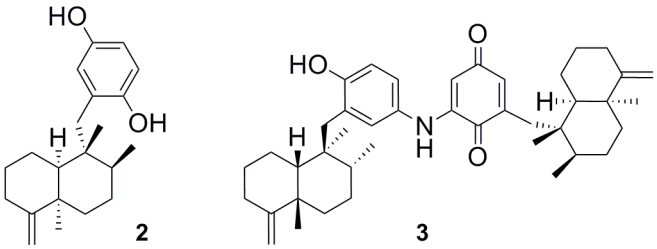


Figure 1.1: Arenarol (**2**) and popolohuanone A (**3**).

The spectroscopic data obtained, suggested that the substitution pattern of the quinone and phenol aromatic ring of **1** were unequivocal. However, the orientation of the monomers to each other through the furan ring could not be deduced. Two possible orientations (**1** and **4**) were proposed (Figure 1.2).

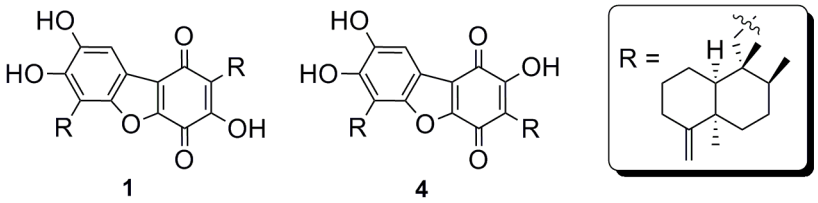


Figure 1.2: Possible orientations of monomers (**1** and **4**).

The reported carbonyl carbon shifts of two compounds (**5** and **6**) prepared *via* unambiguous synthetic routes were compared to the data obtained for **1**. Popolohuanone E (**1**) shows carbonyl carbon chemical shifts at δ 170.8 and 182.7, which fits the data for quinone **5** (δ 171.9 and 182.7). This data therefore supports the proposed structure of **1** (Figure 1.3).[4]

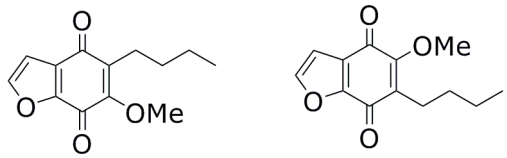


Figure 1.3: Analogues used in ^{13}C NMR comparisons (**5** and **6**).

Since the collection of this data, the structure of **2** including its relative stereochemistry was revealed by X-ray crystallographic analysis of the corresponding

diacetate.[2] The absolute configuration was subsequently established by extensive chemical correlation.[5] Comparison of the data obtained for popolohuanone E (**1**) with that for **2** has subsequently led to the assumption that **2** has an identical stereochemical configuration to **1**. From this, it has been assumed that the absolute stereochemical assignment for popolohuanone E (**1**) is correct.

The bioactivity of **1** is of interest since it inhibits the topoisomerase II enzyme at a relatively low concentration (IC_{50} = 400 nM) and is cytotoxic (IC_{50} = 2.5 μg/mL) to A459 non-small cell lung cancer cells. In addition, **1** shows low cytotoxicity (> 20 μg/mL) to CV-1 non-tumor monkey kidney or HT-29 human colon tumour cells and is marginally cytotoxic to P388 murine leukemia cells (IC_{50} = 20 μg/mL). The inhibitory concentrations of **1** in the topoisomerase II and A459 bioassays are comparable to other anticancer agents currently in clinical use for lung cancer.[6]

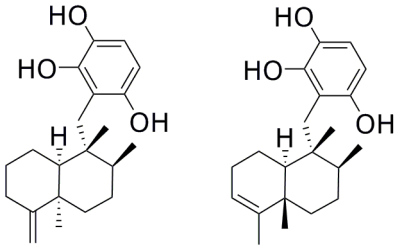
Topoisomerases work by removing helical twists in DNA strands to help prevent coiling or knotting during replication and it is known that type II topoisomerases work by cutting both strands of the DNA helix simultaneously.[7] Topoisomerases are the target enzymes for several of the most effective agents against lung cancer,[8] of which there are two distinct human phenotypes, small cell and non-small cell lung cancer.[9] It is known that small cell lung cancer cells are more responsive to treatment, but account for the minority of lung cancer cases. Topoisomerase II inhibitors are structurally diverse but usually consist of a planar aromatic ring system that can intercalate between DNA base pairs, thus obstructing normal DNA functions such as replication. Due to its planar tricyclic aromatic core, popolohuanone E (**1**) probably falls into this category.

1.2 Proposed Biosynthesis

Current progress in understanding marine organisms is providing more rational guidelines for the selection of potential sources of bioactive secondary metabolites.[10] Sponges are the most primitive multicellular organisms, which capture and digest organic molecules to produce metabolic energy. Their chemical constituents, in particular their secondary metabolites and their structure and function, have attracted the most attention regarding several aspects of organic chemistry. One of the most

widespread groups of constituents found in sponges are terpenoid-quinones and hydroquinones such as popolohuanone E (**1**) and arenarol (**2**).

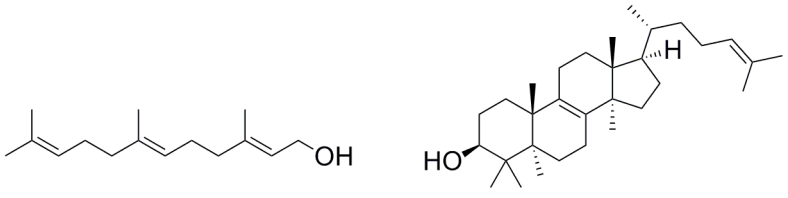
It has been suggested that the structure of **1** could be derived in nature from a dimerisation of two phenolic derivatives.[1] It was postulated that this could take place *via* an enzymatic or possibly non-enzymatic oxidative dimerisation of the unreported 6'-hydroxyarenarol (**7**). In support of this hypothesis, it is known that 6'-hydroxyavarol (**8**) which is an isomer and epimer of **7** and very similar in structure to **2**, has also been isolated from *Dysidea cinerea* (Figure 1.4).[11] With the proposed precursor to popolohuanone E (**1**) yet to be isolated in nature, it is assumed that an immediate dimerisation of 6'-hydroxyarenarol (**7**) could occur to afford naturally occurring popolohuanone E (**1**).



7 **8**

Figure 1.4: 6'-hydroxyarenarol (**7**) and naturally occurring 6'-hydroxyavarol (**8**).

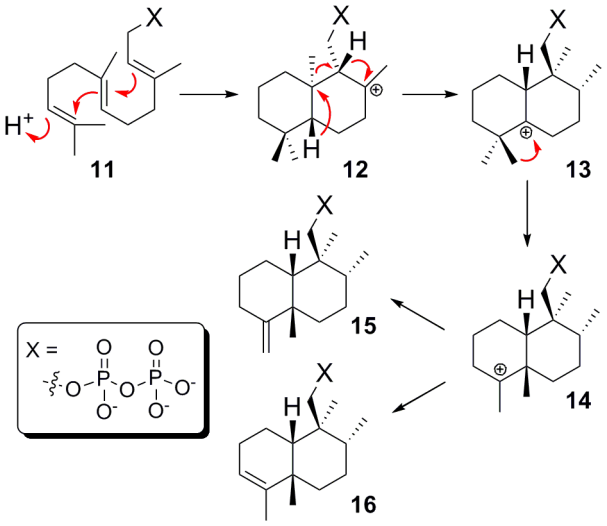
In addition to its unique tricyclic central core, popolohuanone E (**1**) consists of two identical sesquiterpene or *cis*-decalin units. Sesquiterpenes are a diverse group of terpenoid compounds containing a 15 carbon skeleton. Their structural diversity and pharmacological activity makes them of particular interest for use in biology and chemical synthesis. Farnesol (**9**) is the primary precursor to a wide variety of sesquiterpene structures. The formation of **9** is significant due to the dimerisation of farnesyl pyrophosphate (**11**), which has been shown to lead to a variety of important triterpene compounds including lanosterol (**10**), a common precursor to many steroids (Figure 1.5).[12]



Farnesol (**9**) Lanosterol (**10**)

Figure 1.5: Sesquiterpenes farnesol (**9**) and lanosterol (**10**).

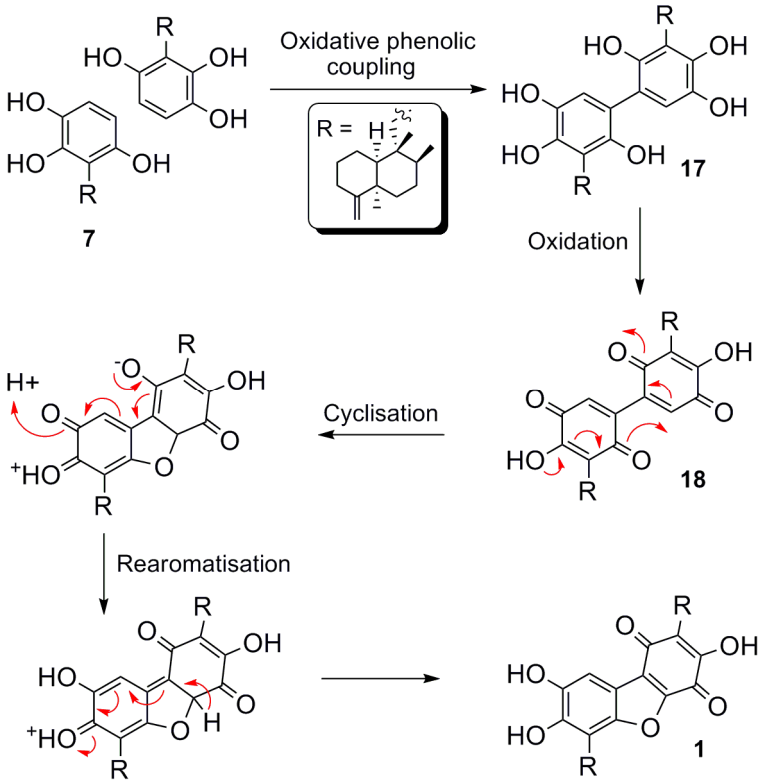
The formation of bicyclic sesquiterpenes similar to the structures found in popolohuanone E (**1**) and arenarol (**2**) are thought to originate from 2-*cis*-6-*trans*-farnesyl pyrophosphate (**11**) or the corresponding 2-*trans*-6-*trans* compound, which are regarded as the biological precursors to almost all sesquiterpene compounds.[13] Cyclisation of **11** gives decalin cation **12**, which can be converted into the key intermediate **13** by a series of concerted hydride and methyl shifts. A further 1,2-methyl shift can then occur giving rise to a *cis* or *trans* decalin cation **14**. Loss of a proton will then result in the formation of either the corresponding *exo*-cyclic **15** or *endo*-cyclic alkene **16** (Scheme 1.0).



Scheme 1.0: Biosynthesis of bicyclic sesquiterpenes.

1.3 Biomimetic Retrosynthetic Analysis

Although there has been no detailed mechanism published for the formation of **1**, Scheuer proposed that oxidative enzymatic or non-enzymatic dimerisation of 6'-hydroxyarenarol (**7**) could be possible.[1] The research in this thesis focuses on a retrosynthetic analysis of **1**, based on this biomimetic approach. Oxidative coupling of two molecules of **7** could provide biaryl **17**, which could undergo further oxidation to afford the intermediate bis-quinone **18**. Cyclisation to give the desired dibenzofuran tricyclic core would complete the target synthesis of popolohuanone E (**1**) (Scheme 1.1).



Scheme 1.1: Proposed biosynthesis of popolohuanone E (**1**).

1.4 Oxidative Phenolic Coupling

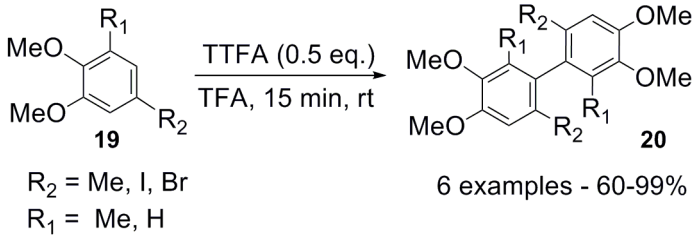
Retrosynthetic analysis of popolohuanone E (**1**), has proposed a key biomimetic oxidative dimerisation of two phenolic units (**7**) (see section 1.3). This strategy would involve a phenolic biaryl coupling reaction as the key step, which have received extensive literature attention in recent years.[14]

The formation of a biaryl bond is a noteworthy transformation for the synthesis of carbon-carbon bonds. The biaryl sub-structure is the central building block in a large number of natural products including lignans, terpenes and alkaloids.[15] The presence of the biaryl structure in chiral ligands for use in asymmetric catalysis,[16] as well as many biologically active natural products,[17] makes them an attractive synthetic target.

Numerous methods for the synthesis of biaryl compounds have been developed including direct coupling, catalysed by a variety of transition metals,[18] Ullmann coupling and metal catalysed cross coupling reactions.[19,20] However, the direct coupling of phenolic compounds still presents a number of challenges. Intermolecular polymerisation of starting materials or products is evident in many oxidative coupling reactions leading to very low yields in some cases.[21] Control of

regioselectivity can also be a challenging prospect, with blocking groups often used to prevent low yields of the desired coupled product. In addition, problems with metal or oxidant insolubility as well as difficulties in separating the inorganic and organic products are often apparent, therefore the use of solid supported oxidants is of particular interest for this type of reaction. The coupling reaction proposed for the synthesis of **1** would require an oxidative dimerisation, therefore this section will concentrate on outlining current examples in oxidative phenolic coupling reactions.

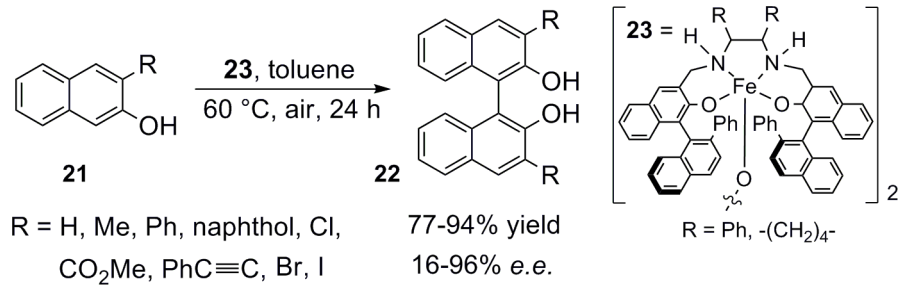
One of the earliest examples of direct oxidative coupling was developed by McKillop *et al.* in 1977.[22] Coupling of protected phenols **19** were successfully performed using thallium(III) trifluoroacetate (TTFA) and trifluoroacetic acid to afford symmetrical biaryls **20** in good yield (60-99%) (Scheme 1.2).



Scheme 1.2: Thallium promoted biaryl coupling.

The scope of the direct biaryl coupling reaction was subsequently expanded to include enzymatic processes,[23] as well as metal catalysed reactions using silver,[24] copper,[25] lead,[26] and in particular a large number of examples have been reported using iron(III) compounds.[27]

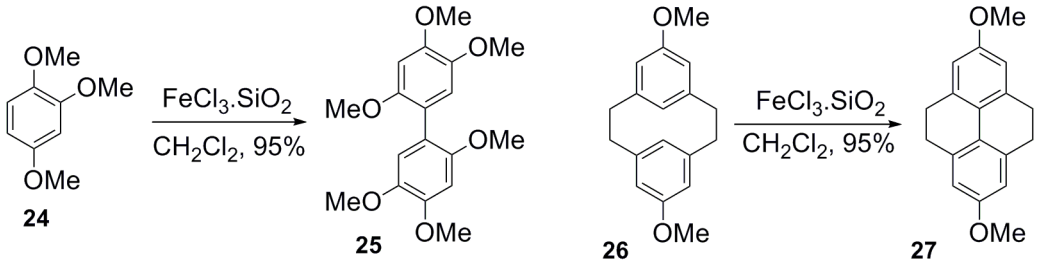
In addition, Katsuki has developed an asymmetric process for the oxidative coupling of 2-naphthols using Fe(salen) complexes.[28] Optimisation of the reaction conditions allowed smooth oxidative coupling to be carried out using 4 mol% of the salen catalyst **23**, in toluene at 60 °C. Oxidative couplings of several 2-naphthol derivatives **21** were examined to afford the desired bi-naphthols **22** in good yield (77-94%) and enantioselectivities (up to 96%) (Scheme 1.3).



Scheme 1.3: Iron catalysed oxidative coupling of 2-naphthols (**21**).

More specifically, many oxidative phenolic processes have made use of iron(III) chloride or 'ferric chloride'. This substance is easily accessible in its anhydrous form and can act as a Lewis acid, activating the phenolic substrates towards dimerisation. It is known that iron(III) chloride can facilitate oxidation, as well as oxidative phenolic coupling *via* a single electron transfer mechanism. In the case of unprotected phenolic substrates (invariably used in biosynthesis), reports in the literature have assumed the initial step to involve formation of a phenoxy radical.[29] Ultimately, a phenolic coupling in our synthesis would be preferred, however our synthetic plan has allowed for the coupling to take place with suitable phenol protection.

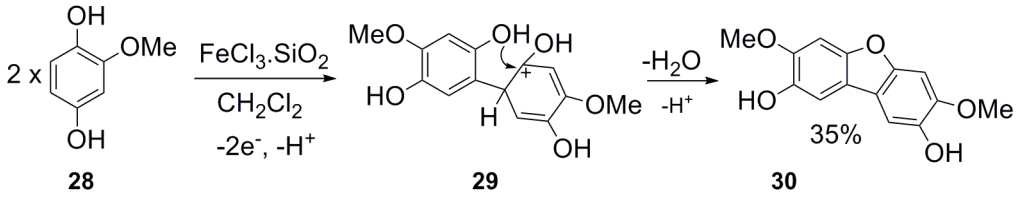
A number of reports in the literature have made use of solid supported ferric chloride, which allows the product to be simply isolated *via* filtration. Studies by Miller *et al.*,[30] demonstrated the use of solid supported $FeCl_3$ as an electron transfer oxidant, providing an effective method for the coupling of phenolic arenes. Experiments were performed using 1.1 equivalents of $FeCl_3.SiO_2$ for the intermolecular case and 2.0 equivalents for the intramolecular reactions, both of which were accomplished in excellent yield (Scheme 1.4).



Scheme 1.4: Intermolecular and intramolecular phenolic coupling.

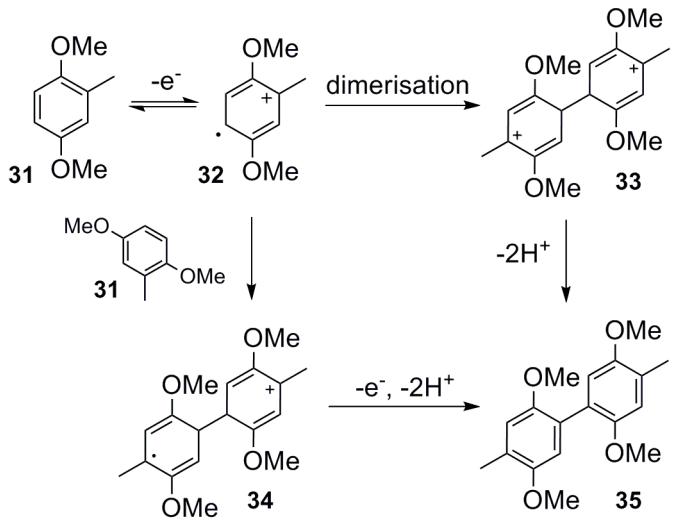
This work also demonstrated that the biaryl products could undergo *in situ* cyclisation to afford tricyclic product **30**. The mechanism was rationalised in terms of electron-

transfer oxidation of phenol **28** followed by dimerisation *para* to the methoxy group, leading to biaryl coupling product **29**. Finally, closure of the furan ring gave dibenzofuran **30**, a moiety also present in the structure of popolohuanone E (**1**) (Scheme 1.5).



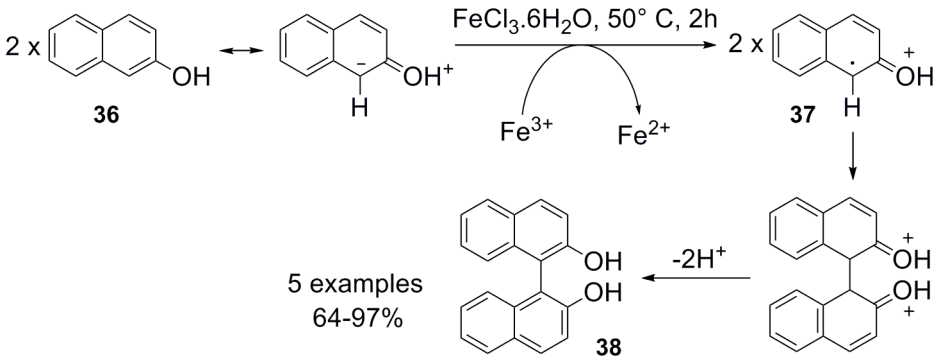
Scheme 1.5: Biaryl coupling followed by cyclisation.

Miller also studied the mechanism of the coupling reaction. He postulated that the process was analogous to electrochemical oxidation, which had been previously studied.[30] Loss of an electron from **31** would give radical cation **32** which could undergo either dimerisation to **33** followed by rearomatisation to afford the desired product **35**, or alternatively, radical cation **32** could react with another molecule of substrate **31**. Further loss of an electron and rearomatisation would also lead to product **35** (Scheme 1.6). It was suggested that each Fe(III) can only accept one electron and that the mechanism therefore involves a series of one-electron transfer steps. When only 1.1 equivalents of $FeCl_3$ was used, the authors suggested that a second electron required to complete the mechanism, could be provided by oxygen present in either the air, or nitrogen, followed by rearomatisation to give the desired biaryl.[31]



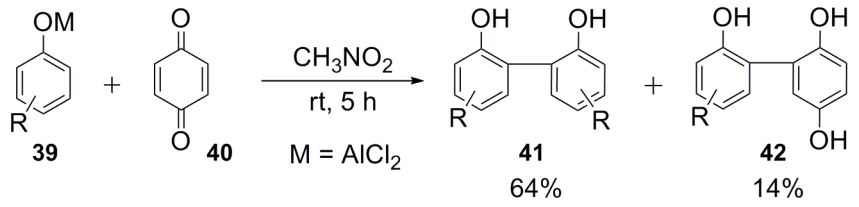
Scheme 1.6: Proposed mechanism for biaryl coupling.

In the late 1980's Toda *et al.* carried out phenolic coupling using 20 mol% iron(III) chloride in the solid state.[32] These reactions were found to proceed faster and more efficiently than those in solution and studies indicated that the reaction could be accelerated by irradiation, when heating to 50 °C. Toda suggested that this method would reduce the amount of polymerisation and undesired quinone by-products. Phenolic coupling was carried out on a variety of substrates **36** using two equivalents of $FeCl_3$ or $[Fe(DMF)_3Cl_2][FeCl_4]$, both of which gave superior yields of coupled product **38** than when carried out in solution, in all cases. The reactions were also performed using 20 mol% of the Fe^{3+} species, which gave yields comparable with the stoichiometric reactions, indicating that oxidation of Fe^{2+} to Fe^{3+} in air, can occur easily in the solid state. In accordance with Miller, Toda also proposed a one electron oxidation of **36** as the initial step to give radical cation **37**, followed by coupling and proton loss to afford the desired products **38** in good yield (Scheme 1.7).



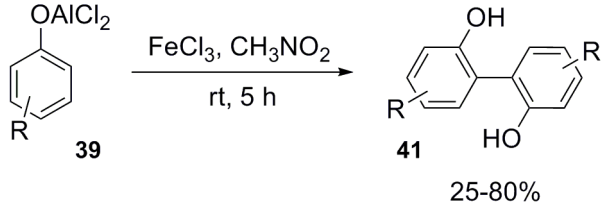
Scheme 1.7: Phenolic coupling in the solid state.

During studies on the regioselective functionalisation of phenols, Satori *et al.*,[33] investigated the oxidative coupling of metal phenolates. Reactions of highly coordinating metal phenolates **39** were carried out in the presence of benzoquinone **40** as the oxidant. In addition to *ortho* oxidative coupling affording symmetrical phenol **41**, (promoted by the quinone), the metal phenolate also reacted with the quinone *via* a 1,4-addition reaction to give biaryl **42** (Scheme 1.8). It was noted that bis-arylation of benzoquinone, affording 2,5-diarylquinones had also been previously described.[34]



Scheme 1.8: Oxidative coupling using metal phenolates.

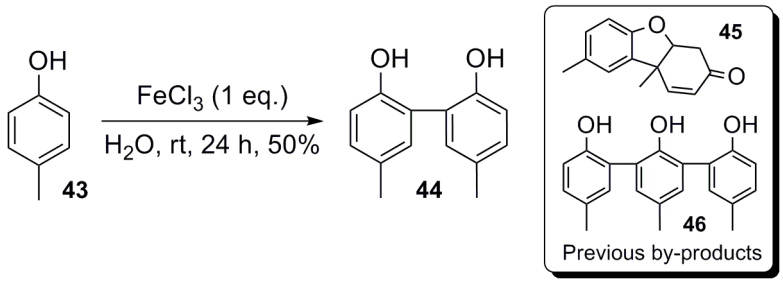
Optimisation of the reaction conditions was then carried out to obtain the symmetrical oxidative coupling products selectively. Reaction of oxygenophilic metal phenolates with appropriate oxidising agents produced the dimeric derivatives in moderate yield. It was noted that when using a free phenol or poorly coordinating phenolate, the production of polymeric material was observed. The authors suggested that use of metal phenolates could enable coordination to both phenols and hence promote successful dimerisation. The use of quinone as an oxidant, produced variable amounts of unwanted addition compound **42**, which was overcome by the use of $FeCl_3$, affording the corresponding products **41** in moderate yield and excellent *ortho* selectivity (Table 1.0).



Entry	R	Yield (%)
1	4-Me	40
2	4-OMe	78
3	4-Cl	25
4	4-*t*-Bu	30
5	4-Ph-OH	32
6	3,4-$(CH=CH)_2$-	77
7	3,4-(-OCH_2O-)	80
8	4-OH	50

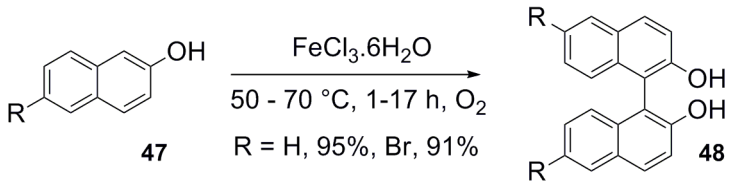
Table 1.0: Phenolate coupling using iron(III) chloride.

One further example demonstrating the use of $FeCl_3$ was reported by Asakura in 1995.[35] Coupling of phenol **43** was carried out in aqueous solution and at high concentration, providing the corresponding bis-phenol **44** in 50% yield. The authors suggested that high concentration allowed the oxidative dimeric compounds to readily precipitate as oil droplets. This prevented unwanted side reactions, such as the competing *ortho-para* coupling product **45** and further polymerisation to trimeric product **46** (Scheme 1.9).



Scheme 1.9: *Ortho* oxidative coupling with iron(III) chloride.

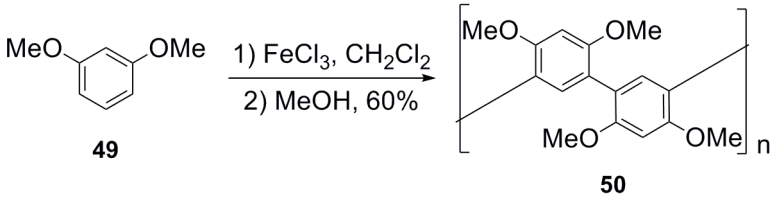
Many reports involving phenolic couplings are conducted on naphthol derivatives, due to their significance as chiral ligands.[36] In 1996, Ding *et al.* developed a biphasic coupling of 2-naphthols suspended in aqueous Fe^{3+} solution.[37] The reactions were performed in aqueous media using $FeCl_3.6H_2O$ and were found to proceed much faster and more efficiently than in homogeneous solution. It was suggested that previous reactions carried out in organic media, led to the production of large amounts of quinone by-products. Ding's mechanism postulated that one molecule of **47** could be consumed by one equivalent of Fe^{3+}, to provide the corresponding intermediate radical cation. This could then react with another neutral molecule of **47** to form the desired C-C bond, followed by proton loss and rearomatisation to afford the bis-phenol **48** (Scheme 1.10).



Scheme 1.10: Coupling of naphthols using iron(III) chloride.

In addition to many examples utilising an aqueous media, Bushby *et al.*,[38] showed that a ferric-chloride, dichloromethane/methanol system worked well for the oxidative coupling of protected phenolic compounds. The results obtained for

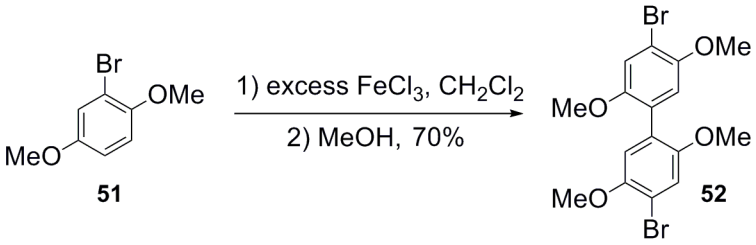
dialkoxybenzene derivatives appeared to depend on the substitution pattern of the aromatic ring. The use of *meta*-dialkoxybenzene derivative **49**, was shown to form polymer **50** (Scheme 1.11).



49 **50**

Scheme 1.11: *meta*-substituted phenolic coupling.

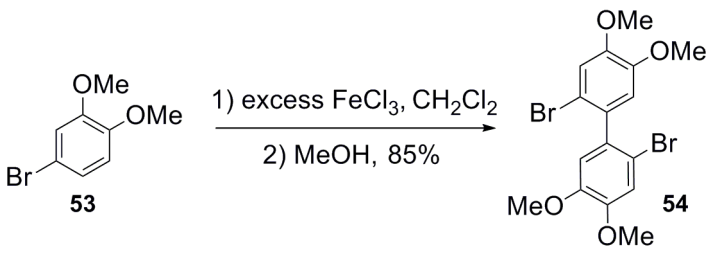
In contrast, when using *para* substituted dialkoxybenzene substrates, isolation of the corresponding dimer product was possible, however in low yield. Similarly, Nishinaga *et al.*,[39] had previously shown poor yields of 1,4-dimethoxybenzene coupling when using aluminium trichloride. It was presumed that the low yield was due to the tendency to carry out further coupling reactions. Hence, when potentially reactive sites were blocked with a bromine, the yield of biphenyl was much improved and oxidation of 2-bromo-1,4-dimethoxybenzene **51** using the ferric chloride–dichloromethane/methanol system, afforded the biphenyl **52** in an excellent 70% yield (Scheme 1.12).



51 **52**

Scheme 1.12: *para*-substituted phenolic coupling.

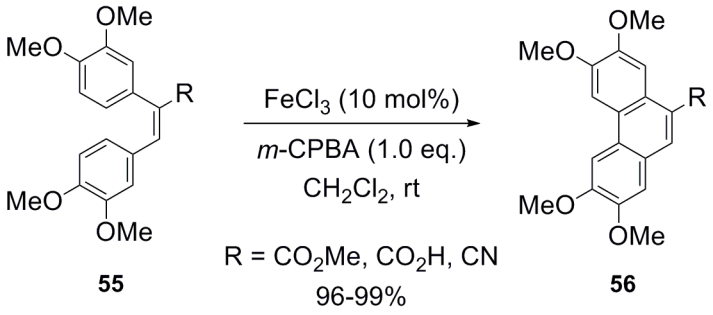
Simple *ortho*-dialkoxybenzenes were also found to afford the corresponding trimer product. However, use of a blocking group at the 4 position forced the reaction to stop at the biphenyl stage, allowing successful coupling of 4-bromo-veratrole **53** to afford biphenyl **54** in 85% yield (Scheme 1.13).



53 **54**

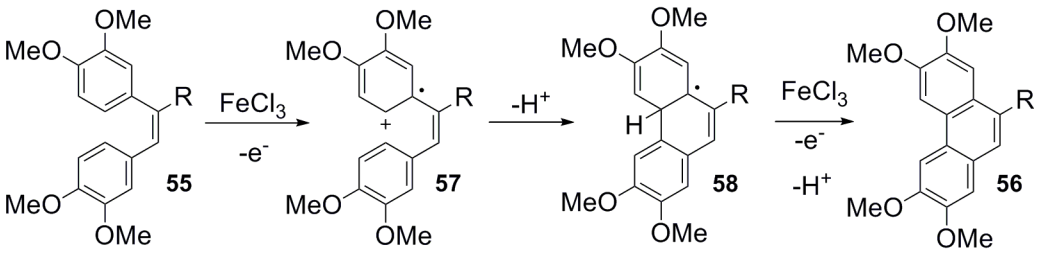
Scheme 1.13: *ortho*-substituted phenolic coupling.

The most recent example of oxidative phenolic coupling promoted by iron(III) chloride, involves the formation of phenanthrene derivatives.[40] In this case iron chloride (10 mol%) was used to carry out intramolecular coupling reactions of arene **55** to generate phenanthrenes **56** in excellent yield. Oxidation was carried out using *m*-CPBA to regenerate the $FeCl_3$ (Scheme 1.14).



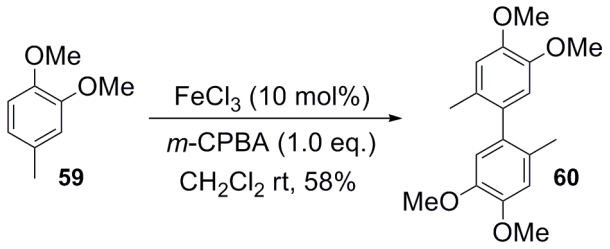
Scheme 1.14: Intramolecular coupling with catalytic iron(III) chloride.

Under the reaction conditions it was found that at least three methoxy groups were necessary for intramolecular coupling to take place and that no reaction was observed when two or less alkoxy groups were present on the substrate. Mechanistic studies for the reaction also suggested the presence of a radical species. When the reaction was performed with the addition of a radical scavenger, the yield of coupled product reduced significantly from near quantitative, to just 11%. In addition, ESR (electron spin resonance) spectra were recorded, showing signals assignable to radical species derived from the starting material. This is consistent with previous suggestions involving the one electron transfer from substrate to $FeCl_3$ to produce Fe^{2+} and radical cation species **57**. This could then undergo electrophilic attack of another electron rich phenyl ring to form the required biaryl bond. Finally, loss of a further electron and dehydro-aromatisation would give the desired tricyclic compound **56** (Scheme 1.15).



Scheme 1.15: Proposed mechanism of the $FeCl_3$ catalysed reaction.

In an extension of this work, intermolecular couplings were also carried out using both 2-naphthol derivatives and methyl ether protected phenols **59**. This afforded the corresponding BINOL or biaryl derivatives **60** in moderate yields (Scheme 1.16).[40]

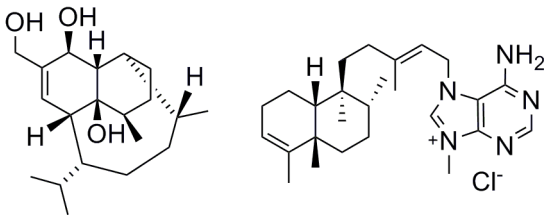


Scheme 1.16: Intramolecular iron(III) chloride promoted oxidative coupling.

This section has highlighted many successful examples of oxidative coupling reactions using iron(III) chloride. This provides a sound basis for the use of this reagent with unprotected phenolic substrates and hence could allow the proposed oxidative coupling for the biomimetic synthesis of popolohuanone E (**1**), to be carried out (see section 1.3).

1.5 Synthesis of cis-Decalins

The decalin moiety can exist in either the *cis* or *trans* form and it is known that the *trans* isomer is energetically more stable due to fewer steric interactions. Despite this, the *cis*-decalin framework is present in the molecular structure of numerous classes of natural products, including *cis*-clerodanes,[41] and cadinanes,[42] both of which exhibit interesting biological activity. Specific examples include vinigrol (**61**),[43] isolated from the fungal strain *Virgaria nigra*, which was found to decrease arterial blood pressure and inhibit platelet aggregation in rats. In addition, agelasine A (**62**), a diterpene alkaloid isolated from the marine sponge *Agelus nakamurai*,[44] exhibits antimicrobial activity and strongly inhibits the Na, K-ATPase enzyme (Figure 1.6). The structure of popolohuanone E (**1**) contains two identical *cis*-decalin units, each of which contain four contiguous stereocentres and is therefore an interesting synthetic challenge.



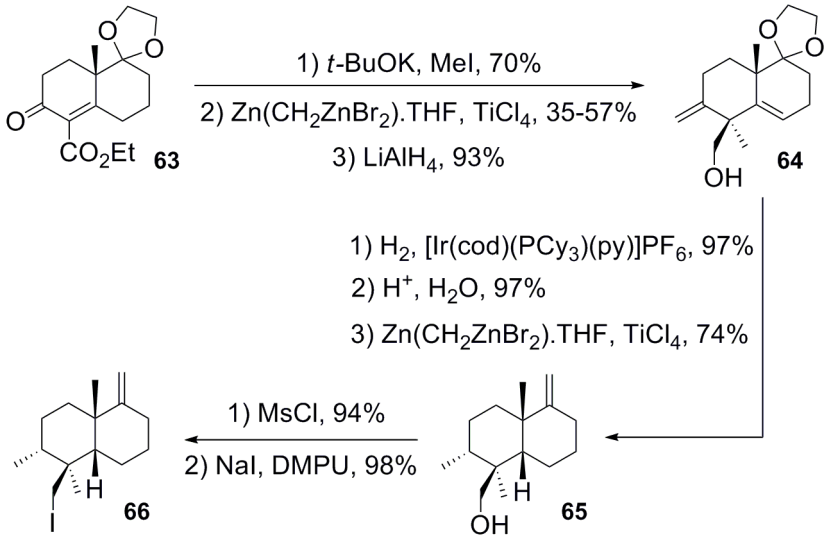
Vinigrol (**61**) Agelasine A (**62**)

Figure 1.6: *Cis*-decalin containing natural products.[45]

Many strategies for the synthesis of the *cis*-decalin framework have made use of the well known Wieland-Miescher type ketones.[46] In addition, the Robinson annulation, Diels-Alder reaction, Cope rearrangement and various cyclisation methods have also been widely used for the construction of the *cis*-decalin structure. With the broad range of natural products containing this moiety, these methods have been studied and reviewed extensively.[47] The following section describes a number of these methods which are particularly relevant to popolohuanone E (**1**) and structurally similar molecules.

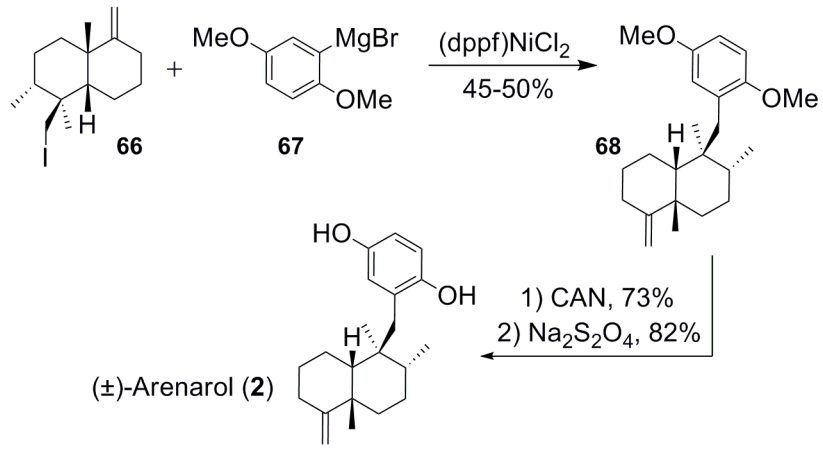
In 1995, Weimer and Scott utilised the Wieland-Mischer ketone in their total synthesis of (±)-arenarol (**2**), which exhibits an identical *cis*-decalin system to that found in **1** (see section 1.1).[48] Their approach began with known decalin **63**, which underwent smooth methylation using MeI and *t*-BuOK in 70% yield. Subsequent reaction with Nysted's reagent, afforded the corresponding *exo*-cyclic olefin in moderate 35-57% yield. On treatment with $LiAlH_4$, this provided the *neo*-pentyl alcohol **64**, in 93% yield (Scheme 1.27).

Stereoselective hydrogenation using Crabtree's iridium catalyst under 1000 psi of H_2, afforded a single diastereoisomer of the *cis*-decalin, in virtually quantitative yield. With the *cis* fused rings in place, removal of the dioxolane protecting group and reaction of the resulting ketone with Nysted's reagent, afforded the *exo*-cyclic olefin **65** in excellent yield (74%). Finally, conversion of **65** to the corresponding iodide was accomplished by formation of the mesylate followed by reaction with NaI to provide *neo*-pentyl iodide **66** obtained in 7 steps (21-34% yield) (Scheme 1.17).



Scheme 1.17: Advanced intermediate towards the synthesis of (±)-arenarol (**2**).

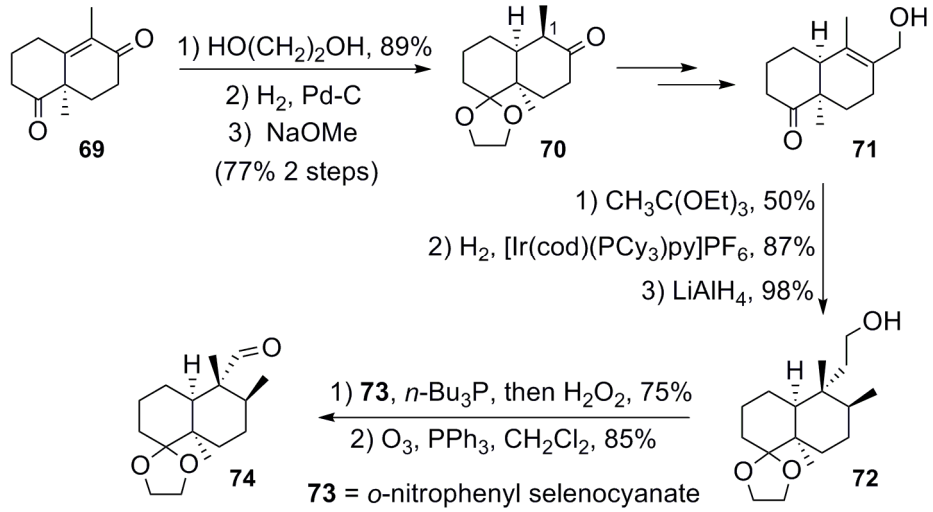
Installation of the phenolic portion present in arenarol (**2**) was then carried out. Treatment of iodide **66** with Grignard **67** in the presence of (dppf)$NiCl_2$ afforded **68** in yields of 45-50%. Subsequent oxidation using CAN in aqueous $NaHCO_3$ and CH_3CN allowed complete conversion to the corresponding *p*-quinone, also known as the natural product arenarone, isolated from the *Dysidea arenaria* sponge.[2] Finally, mild reduction of arenarone with sodium hydrosulfite, gave the target (±)-arenarol (**2**). This methodology demonstrates an efficient synthesis involving formation of a C-C bond at a *neo*-pentyl centre (Scheme 1.18).



Scheme 1.18: Final steps towards (±)-arenarol (**2**).

Later in 1997, Terashima and Katoh *et al.*, synthesised (+)-arenarol (**2**) enantioselectively from enantiomerically pure Wieland-Miescher (-)-ketone (**69**).[49] Initial investigations focused on the *cis*-fused segment. Chemoselective ketone protection and stereocontrolled hydrogenation of the resulting acetal gave exclusively

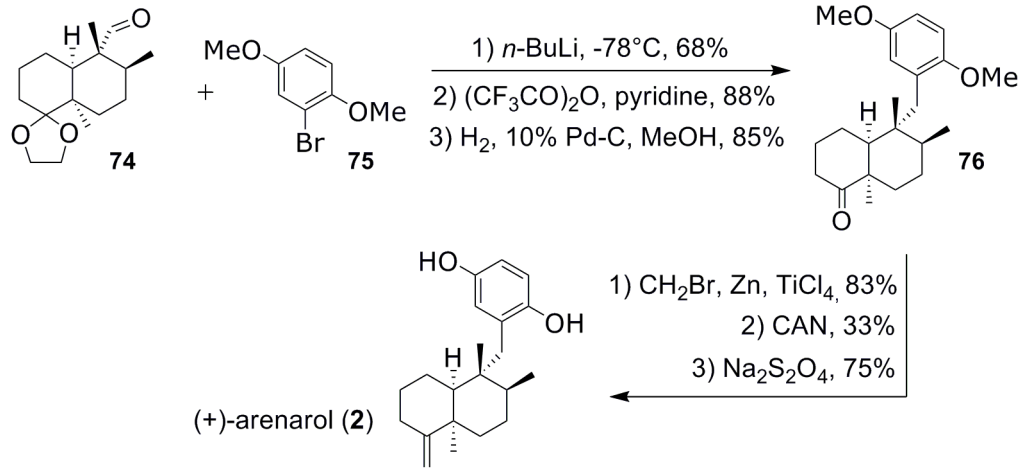
the *cis*-decalin, but as a 13:1 mixture of C1 epimers. Successful base catalysed epimerisation to the more thermodynamically stable compound was then carried out, to afford **70** in 77% over two steps. With this in place, subsequent functional group interconversions, followed by removal of the ketal protecting group, allowed formation of allylic alcohol **71**. With this in hand, Claisen rearrangement was achieved using triethylorthoacetate, giving rise to a 3:2 mixture of stereoisomers, separated using silica gel chromatography. The remaining stereocentres were introduced *via* stereocontrolled hydrogenation of the resulting alkene, using Crabtree's iridium catalyst to provide a single stereoisomer in 87% yield. This was followed by reduction to the corresponding alcohol **72** in 98%. Methylenation was then achieved using *o*-nitrophenyl selenocyanate and tri-*n*-butyl phosphine, followed by treatment with 30% hydrogen peroxide (72% over 2 steps). Finally ozonolysis of the terminal alkene furnished target intermediate **74** in 85% yield (Scheme 1.19).



Scheme 1.19: Decalin segment of (+)-arenarol (**2**).

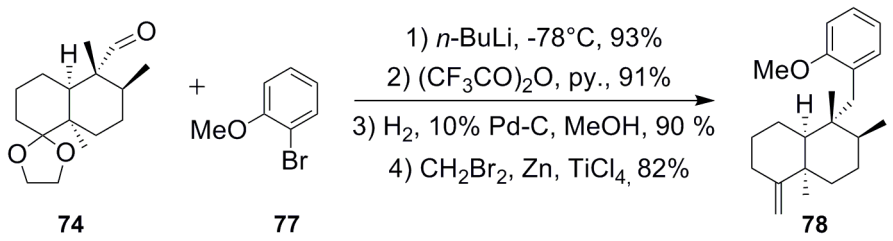
With the *cis*-decalin portion in hand, treatment of commercially available 1-bromo-2,3-dimethoxybenzene **75** with *n*-butyllithium, followed by addition of the aldehyde **74**, proceeded smoothly in 68% yield. Benzylic deoxygenation *via* formation of the trifluoroacetate followed by hydrogenolysis was achieved successfully. These conditions also facilitated removal of the ketone protecting group to afford **76** in 72% yield over two steps. Subsequent direct methylenation using Nysted's conditions, allowed formation of the corresponding olefin in 83%. The final two steps were carried out as in Weimer and Scott's racemic synthesis.[49] Treatment with CAN afforded the corresponding quinone (arenarone), followed by reduction with sodium

hydrosulfite, to furnish the target natural product (+)-arenarol (**2**), in 25% yield over two steps. This was much lower than the 60% achieved in Weimer and Scott's synthesis (Scheme 1.20).



Scheme 1.20: Final steps towards (+)-arenarol (**2**).

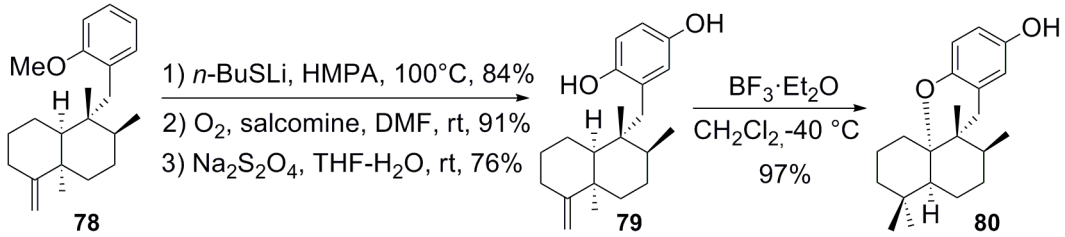
Later in 2002, Katoh *et al*., utilised their *cis*-decalin synthesis in an efficient total synthesis of (+)-aureol (**80**).[50] Katoh envisioned that (+)-aureol (**80**) could be produced biomimetically by an acid-promoted rearrangement of (+)-arenarol (**2**). To this end previously synthesised aldehyde (**74**) was reacted with lithiated 2-anisole (**77**) (generated *in situ*) to give the corresponding alcohol. Subsequent transformations, similar to that used in their arenarol synthesis, afforded the desired the *exo*-olefin **78** in 82% yield (Scheme 1.21).



Scheme 1.21: Initial steps towards (+)-aureol (**80**).

Since the *exo*-olefin moiety present in this type of system was known to be labile under acidic conditions,[51] demethylation was performed by treatment with lithium *n*-butylthiolate (10 equivalents) in HMPA, which led to successful formation of the corresponding phenol in 84% yield. Late stage installation of the remaining hydroxyl group was achieved by reaction with molecular oxygen and salcomine (1.0 equivalent), to give the intermediate quinone. This was followed by reduction as

carried out previously, using sodium hydrosulfite, to afford the sub-target arenarol (**79**). Focus then turned towards the crucial acid-promoted rearrangement. This was found to proceed effectively by treatment with boron trifluoride etherate, which led to the formation of (+)-aureol (**80**) in 97% yield (Scheme 1.22). Fortunately, no isomeric products (*trans*-fused decalin structures) were obtained in the rearrangement/cyclisation reaction.



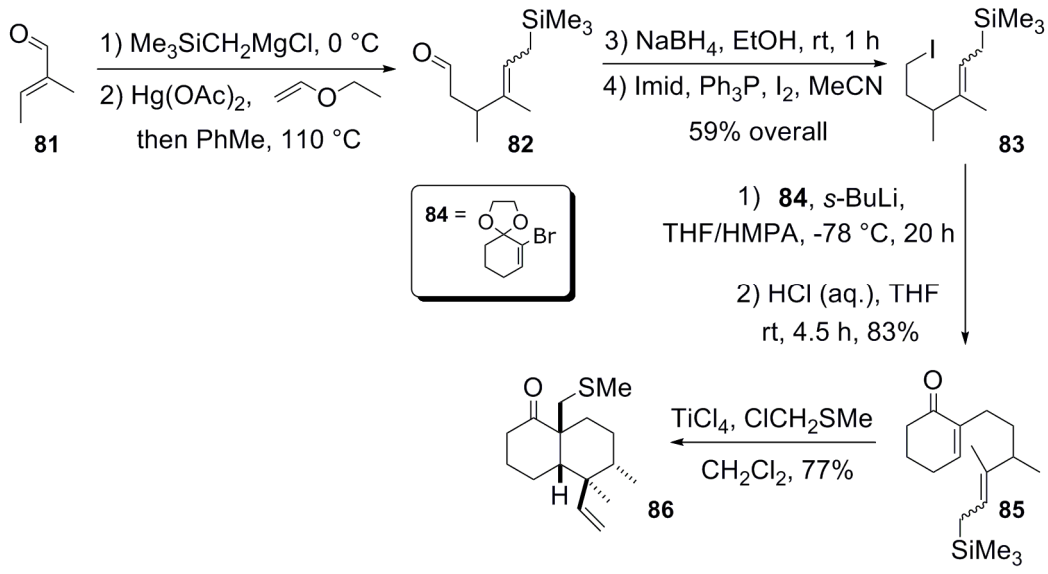
Scheme 1.22: Final stages towards (+)-aureol (**80**).

Finally, within the Anderson group, an alternative strategy for the synthesis of popolohuanone (**1**) was underway. Investigations initially began with a formal synthesis of (±)-arenarol (**2**),[52] which in contrast to previous syntheses, constructed the *cis*-decalin *via* a key intramolecular Hosomi-Sakurai reaction. This had previously been developed in the early 1980's by Tokoroyama, for the synthesis of the *cis*-clerodane natural product linaridial.[53]

To explore the proposed Hosomi-Sakurai reaction, bromide **84** was synthesised in two steps from commercially available cyclohexenone. Synthesis of the required allylsilane portion was then investigated. Tiglic aldehyde **81** was treated with Me_3SiCH_2MgCl followed by Claisen rearrangement of the resulting alcohol using $Hg(OAc)_2$ in ethyl vinyl ether, to afford aldehyde **82**. Reduction with $NaBH_4$, followed by conversion of the hydroxy group to the corresponding iodide gave **83** in 59% overall yield. The use of a one-pot iodination using triphenylphosphine, iodine and imidazole was found to substantially increase the overall yield of this transformation as opposed to using the reported two-step procedure.[53]

Treatment of bromide **84** with two equivalents of *sec*-butyllithium, followed by quenching of the resultant alkyllithium with alkyl iodide **83** gave the desired allylsilane. Removal of the ketal protecting group, afforded the Hosomi-Sakurai precursor **85** in 83% yield over two steps, as a 5:4 mixture of *E*/*Z* isomers. Intramolecular Hosomi-Sakurai cyclisation mediated by titanium tetrachloride, with

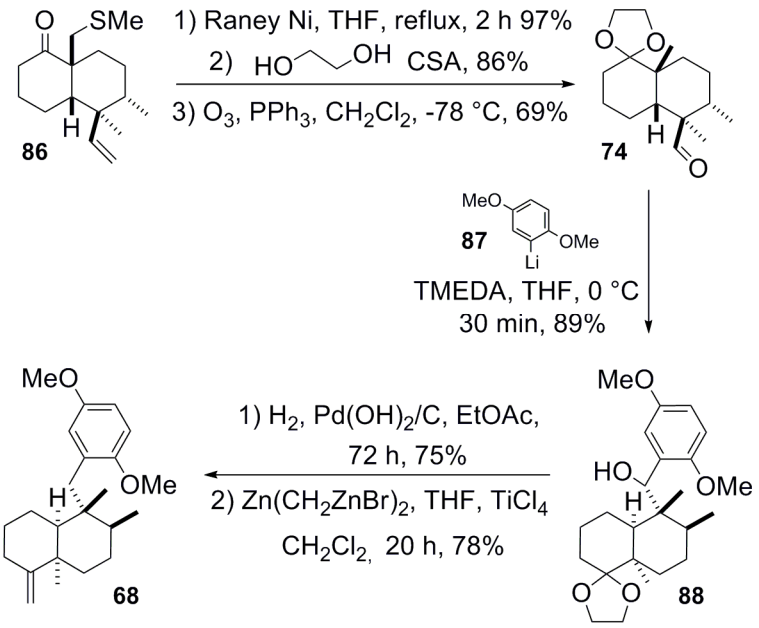
in situ trapping of the resultant enolate with $ClCH_2SMe$, formed the desired *cis*-decalin **86** stereoselectively in 77% yield (Scheme 1.23).



Scheme 1.23: Anderson's formation of the *cis*-decalin system.

With the proposed key Hosomi-Sakurai reaction proving successful, *cis*-decalin **86** was transformed into the requisite aldehyde **74**. Desulfurisation using deactivated Raney nickel (97%), followed by protection of the ketone gave the corresponding ketal in 86% yield. Subsequent ozonolysis of the terminal alkene afforded aldehyde **74** in 69% yield.

Installation of the phenolic group was carried out *via* reaction with *ortho*-lithiated-1,4-dimethoxybenzene **87** to afford alcohol **88** in an excellent 89% yield as an inseparable, unquantifiable mixture of diastereoisomers. Hydrogenation conditions for deoxygenation were carried out successfully, allowing isolation of the ketone in 75% yield. Finally, treatment with Nysted's reagent and $TiCl_4$ afforded the *exo*-cyclic alkene **68** in 78% yield, completing the formal synthesis of (±)-arenarol (**2**) (Scheme 1.24).



Scheme 1.24: Formal synthesis of (±)-arenarol (**2**).

With a racemic synthesis of (±)-arenarol (**2**) in hand, work within the Anderson group began focusing on the asymmetric synthesis of the proposed precursor to **1**, 6'-hydroxyarenarol (**7**). This would allow synthesis of the core of **1** to be investigated *via* the proposed oxidative dimerisation reaction.

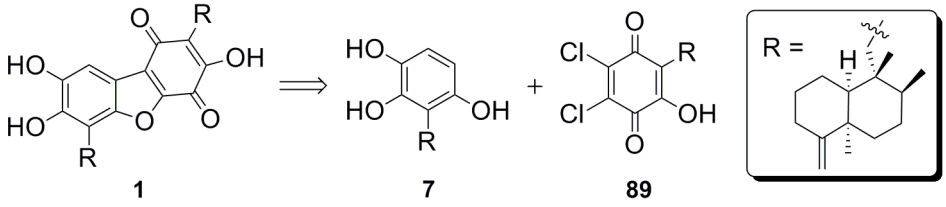
Development of an asymmetric synthesis of **7**, required iodide **83** to be synthesised in enantiopure form. The previous route to iodide **83** required the corresponding allylic alcohol to be generated in enantiomerically pure form and for chirality to be transferred through the Claisen rearrangement. Although it was found that chirality could be transferred through an Ireland Claisen rearrangement,[54] this route eventually proved unsuccessful as subsequent CBS reduction failed to give an *e.e.* of more than 50%. These results led to the development of an alternative route utilising a chiral auxiliary to introduce the crucial methyl stereocentre.[55] This route forms part of the work developed during this research program and is therefore discussed later in greater detail (see section 3.0).

As described above, the development of the *cis*-decalin system present in both arenarol (**2**) and popolohuanone (**1**) has now been studied extensively by a number of groups. With the knowledge and information gained from these studies in hand, work towards the synthesis of the central core and hence the total synthesis of **1** has become the key area of research.

1.6 Approaches to the Tricyclic Core of Popolohuanone E

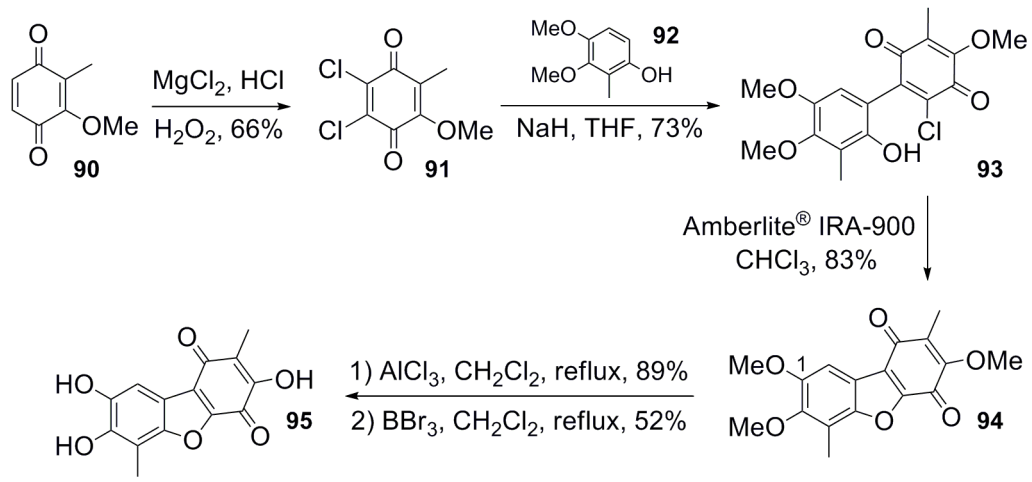
As well as the challenges associated with the *cis*-decalin unit, popolohuanone E (**1**) is of synthetic interest due to its unique tri-hydroxylated dibenzofuran-1,4-dione central core. Investigations into this system have been carried out by three groups besides the Anderson group and their approaches are detailed below.

Katoh began investigations towards the synthesis of **1** in 1996.[56] Retrosynthetic analysis of the central core of **1** featured a biomimetic-type annulation of the phenolic unit **7** with corresponding chloro-quinone **89**, followed by cyclisation to form the central furan ring (Scheme 1.25).



Scheme 1.25: Katoh's approach to popolohuanone E (**1**).

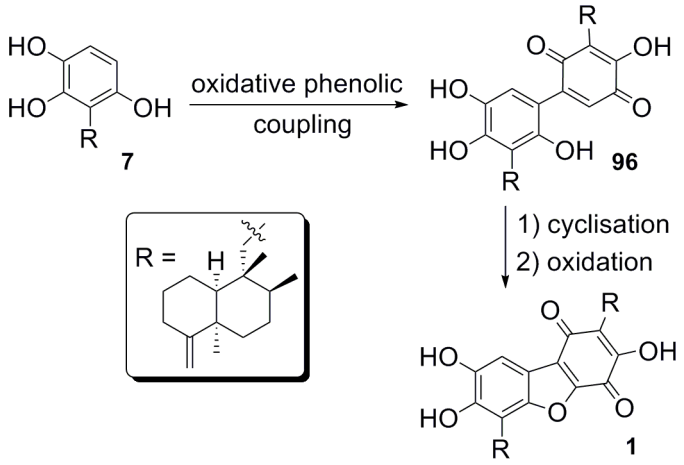
This methodology was initially demonstrated on a suitable model system (**95**) to enable investigation into the proposed regioselective coupling reaction. Quinone **91** was readily prepared from **90** by dichlorination using magnesium chloride and HCl, followed by treatment with hydrogen peroxide in 66% yield.[57] Construction of the dibenzofuran-1,4-dione core was a two-step sequence. Coupling of phenol **92** with quinone **91** was carried out in the presence of sodium hydride, which proceeded smoothly to afford biaryl **93** in 73% yield as a single regioisomer. Subsequent ring closure by exposure to Amberlite® IRA-900, led to successful formation of the central core (**94**) in 83% yield (Scheme 1.26).



Scheme 1.26: Katoh's model system for the core of popolohuanone E (**1**).

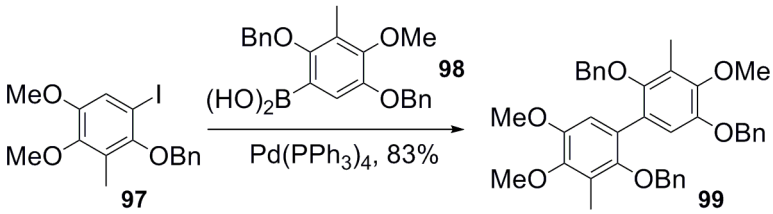
Global methyl ether deprotection was then required to complete the synthesis of the central core. Treatment with aluminium chloride, afforded the corresponding C-1 monomethyl ether, which was further subjected to boron tribromide giving rise to the tricyclic core (**95**) in 52% yield. This method provided strong evidence that the core of **1** could be accomplished *via* this approach. Katoh continued to develop this strategy, which culminated in the synthesis of 8'-*O*-methylpopolohuanone E (**131**) (see section 1.7).

A second approach to the tricyclic core was reported by Benbow, also in 1996.[58] This was also based on the biomimetic strategy first suggested by Scheuer.[1] Oxidative phenolic coupling of **7**, followed by selective oxidation of one arene ring could give biaryl **96**, which Benbow proposed to be the precursor to **1**. Finally, an intramolecular 1,4-addition-elimination process involving loss of a hydride ion, would give popolohuanone E (**1**) (Scheme 1.27).



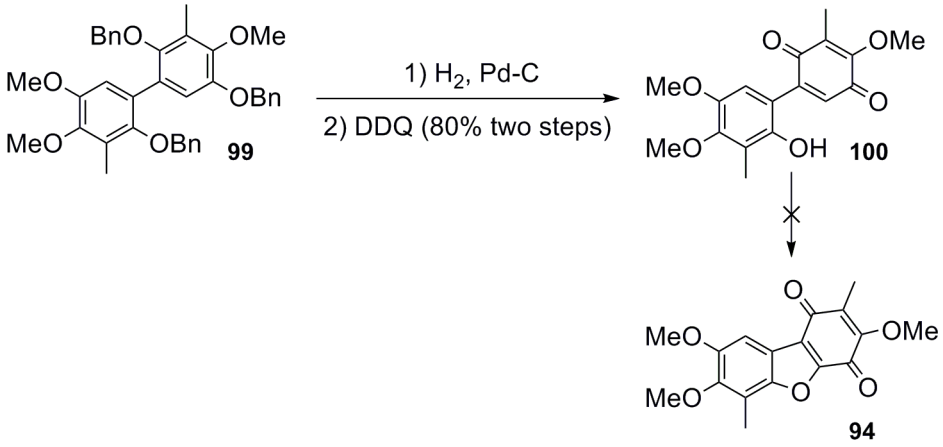
Scheme 1.27: Benbow's proposal for the formation of **1**.

To investigate the proposed synthesis, Benbow studied the formation of the quinodal systems using a Suzuki coupling of aryl halides with aryl boronic acids.[58] The required boronic acids (**98**) were formed by lithium halogen exchange of the corresponding aryl halide followed by addition of a trisalkyl borate and subsequent hydrolysis. Biaryl **99** was subsequently synthesised *via* a Suzuki coupling reaction between aryl iodide **97** and boronic acid **98** in 83% yield (Scheme 1.28).



Scheme 1.28: Suzuki coupling to form biaryl **99**.

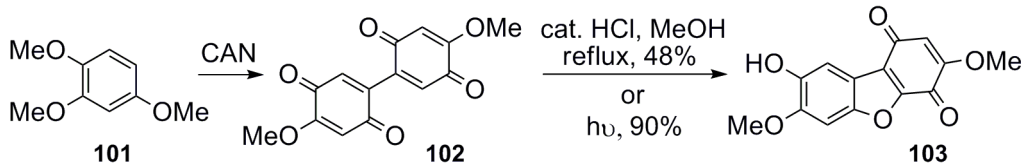
With the biaryl structure in hand, debenzylation was carried out using hydrogenolysis followed by oxidation with DDQ to give hydroxyquinone **100** in 80% yield over two steps. Unfortunately, spontaneous ring closure to form the central core **94** did not occur on this model system. In addition, no cyclisation was seen when treating hydroxyquinone **100** with a series of bases (Et_3N, NaH, KH), or in the presence of a mild acid catalyst (PPTS) (Scheme 1.29).[59]



Scheme 1.29: Attempted construction of the tricyclic core.

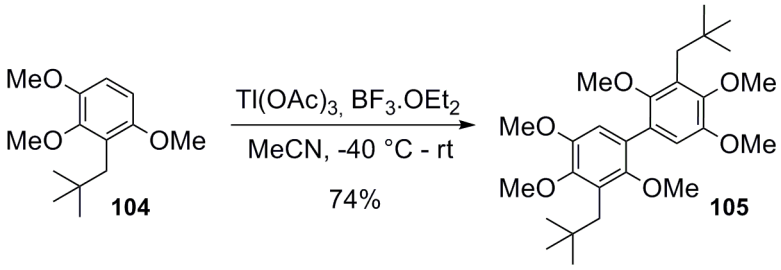
Studies within the Anderson group also focused on a biomimetic approach to the central core of **1**. It was suggested by Scheuer, that oxidative dimerisation of 6'-hydroxyarenarol (**7**) could give the corresponding symmetric bis-quinone **18** which could then rearrange to afford the dibenzofuran central core. Benbow's biomimetic strategy had proved largely unsuccessful, which strengthened the belief that **1** was derived from a bis-quinone precursor rather than the cyclisation of a phenol-quinone structure.

This method has also been supported by reports in the literature. In 1934, Erdtman *et al.*,[60] demonstrated the successful rearrangement of bis-quinones to form tricyclic dibenzofuran derivatives. This was achieved by oxidation of 1,2,4-trimethoxybenzene **101** with excess CAN to give **102**, followed by a thermal acid catalysed rearrangement to afford dibenzofuran **103**. In addition, similar work by Thompson,[61] in 1963 showed the same rearrangement under photochemical conditions (Scheme 1.30).



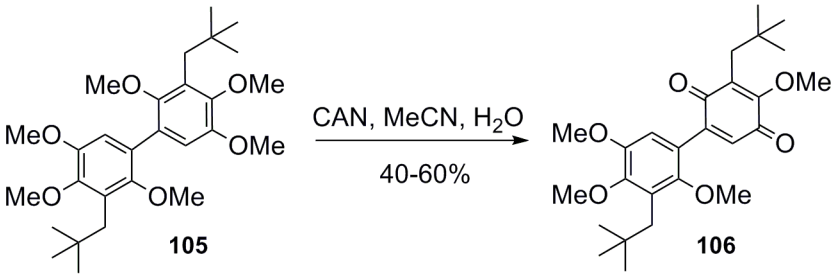
Scheme 1.30: Photochemical and thermal bis-quinone rearrangement.

Within the Anderson group, a simple model system was used to test the feasibility of the biomimetic synthesis.[76] Arene **104** was used as a model for 6'-hydroxyarenarol (**7**), which on treatment with thallium(III) acetate followed by $BF_3.Et_2O$, enabled dimerisation to occur smoothly, affording symmetrical biaryl **105** in 74% (Scheme 1.31).[52]



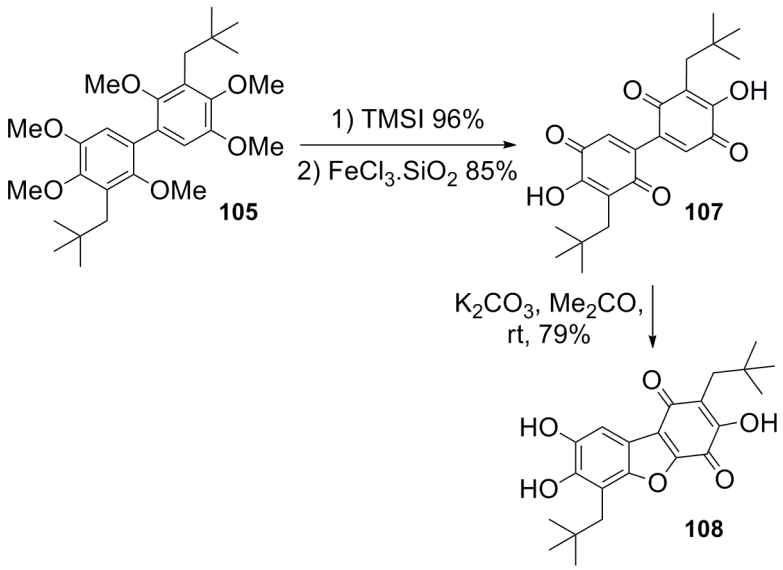
Scheme 1.31: Non-phenolic oxidative coupling.

It is known that the oxidation of 1,4-methoxyphenols can produce the corresponding 1,4-quinones in good yield.[62] Therefore coupled biaryl **105** was treated with CAN under a variety of conditions, however this led to isolation of the corresponding mono-quinone **106** in 40-60%. Unfortunately, all attempts to carry out further oxidisation to the bis-quinone were unsuccessful (Scheme 1.32).



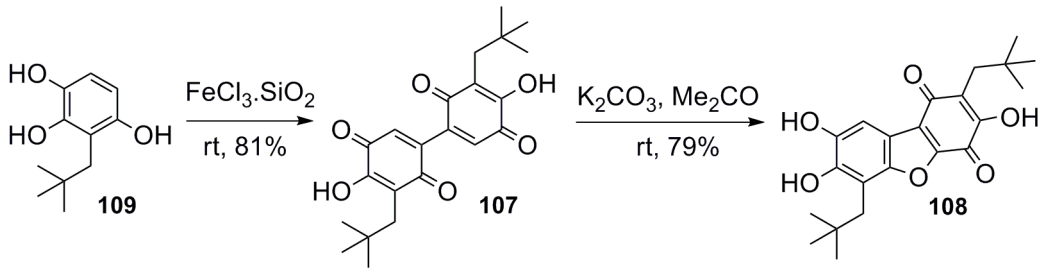
Scheme 1.32: Partial oxidation to mono-quinone **106**.

Due to this result, global demethylation of **105** was carried out successfully using TMSI (96%) and subsequent oxidation using silica supported iron(III) chloride gave the bis-quinone **107** in high yield (85%). Unfortunately, attempted rearrangement to afford the tricyclic core proved ineffective under photochemical conditions and acidic conditions resulted in a very low yield. However, cyclisation to the desired tricyclic core **108** was successful under very mild basic conditions in 79% yield (Scheme 1.33).



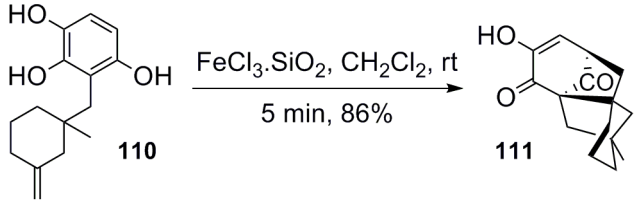
Scheme 1.33: Model study towards the central core.

This synthesis was also demonstrated on unprotected arene **109**. Oxidative coupling afforded bis-quinone **107**, followed by cyclisation with K_2CO_3, which successfully furnished the desired tricyclic core **108** according to the proposed biomimetic strategy (Scheme 1.34).



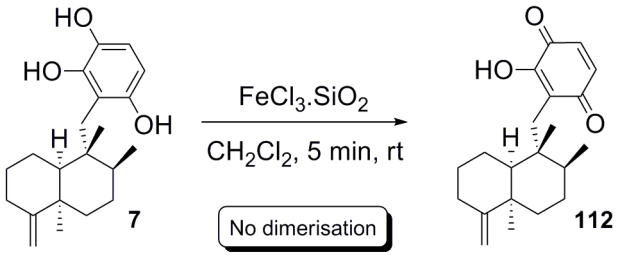
Scheme 1.34: Direct biomimetic synthesis of the tricyclic core.

Model system studies were then continued, incorporating the *exo*-cyclic alkene present in the final target. Phenol **110** was synthesised over 11 steps (see section 3.1) and treated with $FeCl_3.SiO_2$. Unfortunately, under identical conditions to those used previously, only an intramolecular [5+2] cycloaddition product **111** was formed (Scheme 1.35).



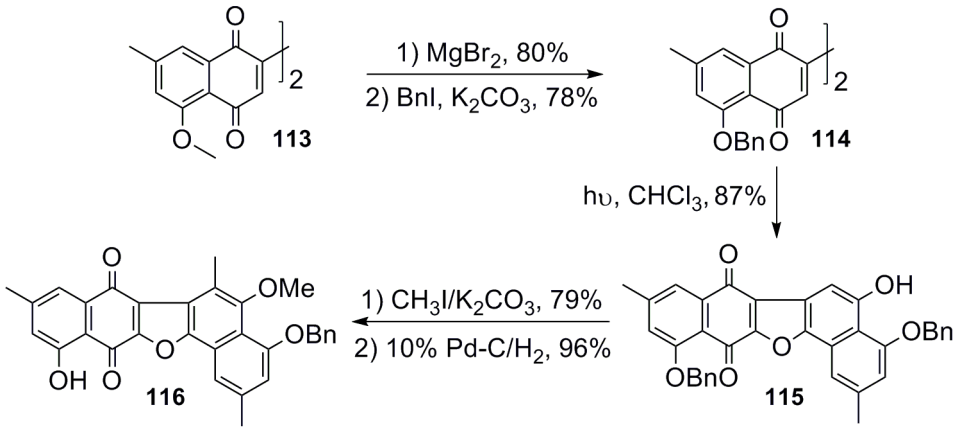
Scheme 1.35: Formation of [5+2] cycloaddition product **111**.

Despite this result, Anderson postulated that the intramolecular reaction would not occur when using 6'-hydroxyarenarol (**7**), as the reactive alkene is much further away from the phenol unit. However, treatment of **7** under the standard $FeCl_3.SiO_2$ conditions (among others) afforded oxidation to the corresponding mono-quinone **112** only (Scheme 1.36).



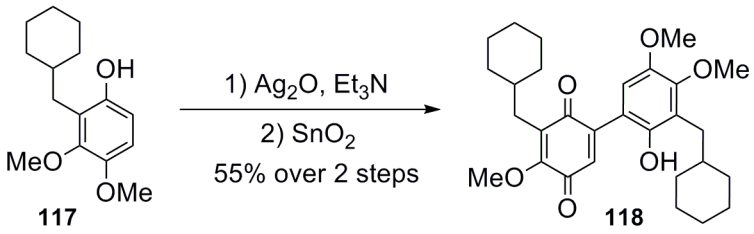
Scheme 1.36: Attempted dimerisation using 6'-hydroxyarenarol (**7**).

The final group interested in synthesising popolohuanone E (**1**) have also concentrated on a biomimetic approach. Takeya *et al*. demonstrated this strategy in a total synthesis of violet-quinone (**116**).[63] This involved a binaphthoquinone key intermediate **113**, which was synthesised *via* a novel oxidative dimerisation with ZrO_2/O_2.[64] Demethylation was performed using $MgBr_2$ to produce natural product biramentaceone in 80% yield, followed by benzylation in the presence of K_2CO_3 to afford cyclisation precursor **114** in 78% yield. Ring closure was then achieved by means of photolysis in $CHCl_3$ to give pentacycle **115** in 87% yield. Finally, methylation followed by reductive deprotection of the benzyl group furnished the desired violet-quinone (**116**) in 96% yield (Scheme 1.37).



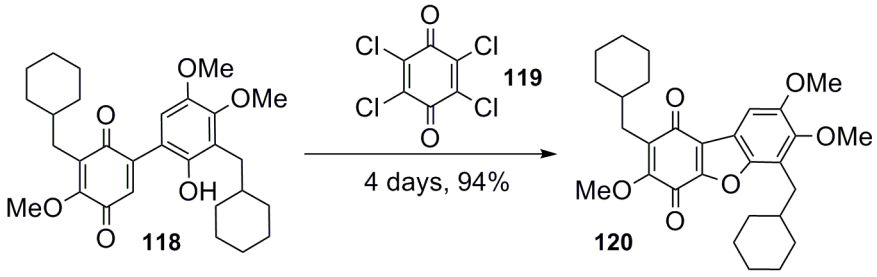
Scheme 1.37: Takeya's biomimetic synthesis of violet-quinone (**116**).

Takeya also investigated the construction of dibenzofuran-1,4-diones *via* oxidative cyclisation of quinone-arenols.[65] The required quinone-arenols **118** were synthesised by a two-step sequence involving oxidative dimerisation of arene **117** with silver(I) oxide, followed by mono-demethylation using SnO_2. This study demonstrated the success of this reaction on examples with substitution patterns similar to that present in popolohuanone E (**1**) (Scheme 1.38).



Scheme 1.38: Preparation of quinone-arenol **118**.

Cyclisation was achieved using either benzo-1,4-quinone or chloranil (**119**) in the presence of molecular oxygen, leading to the desired tricyclic products. A variety of solvents and temperatures were screened and the reaction was found to be most successful when heating in an O_2 saturated toluene solution with chloranil (**119**). Quinone-arenol **118** underwent successful oxidative cyclisation to give **120** in 94% yield over 4 days (Scheme 1.39). This methodology was also applied to the synthesis of violet-quinone **116**, which used benzoquinone in the presence of O_2 to afford the desired natural product.



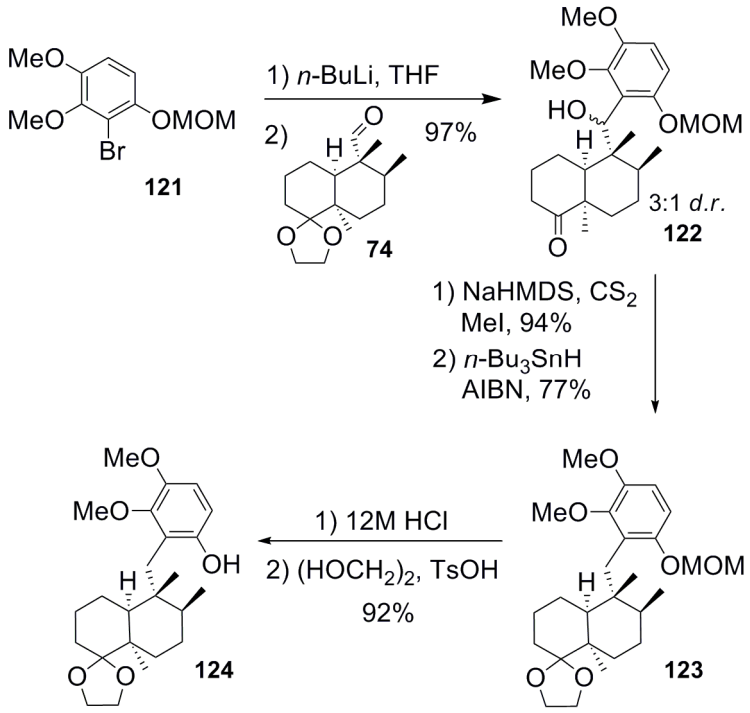
Scheme 1.39: Oxidative cyclisation of quinone-arenols.

1.7 Katoh's 8-O-Methylpopolohuanone E

Katoh *et al.*, had previously generated a synthetic pathway to compounds containing a 3,7,8-trihydroxydibenzofuran-1,4-dione core, which represents the central ring system present in **1** (see section 1.6).[56] This work eventually led to the asymmetric

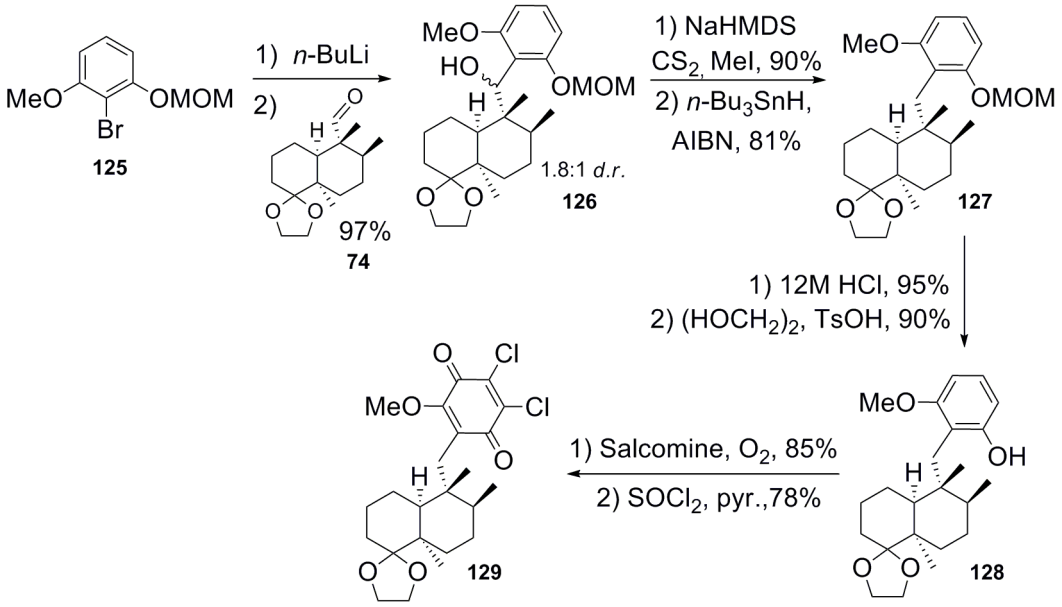
synthesis of 8-*O*-methylpopolohuanone E (**131**) in 2001 and is the closest synthesis towards popolohuanone E (**1**) to date.[66]

As previously reported, retrosynthetic analysis of **1** featured a biomimetic-type annulation of a phenolic segment with a corresponding quinone. Synthesis of the phenolic portion **124** was carried out from the known Weiland-Miescher diketone, previously used in their asymmetric synthesis of (+)-arenarol (**2**) (see section 1.5).[49] Lithiation of 1-bromo-2,3-dimethoxy-6-(methoxymethoxy)benzene **121**,[67] with *n*-butyllithium was carried out and the resulting aryllithium reacted with *cis*-decalin aldehyde **74** affording **122** in 97% as a 3:1 mixture of epimeric alcohols (Scheme 1.40). Subsequent removal of the sterically hindered hydroxyl group was best achieved by applying Barton-McCombie deoxygenation conditions.[68] Therefore, alcohol **122** was subjected to sodium bis-(trimethylsilyl)amide followed by carbon disulfide and iodomethane to furnish the corresponding methyl xanthate in 94% yield. This was further treated with tributyltin hydride and AIBN, which provided the desired deoxygenated product in 77% yield. Finally, conversion to the phenolic coupling precursor involved a two-step sequence. Acid hydrolysis of both the MOM and ethylene acetal protecting groups, followed by re-protection of the carbonyl functionality gave **124** in 92% yield over 2 steps (Scheme 1.40).



Scheme 1.40: Katoh's synthesis of the phenolic segment **124**.

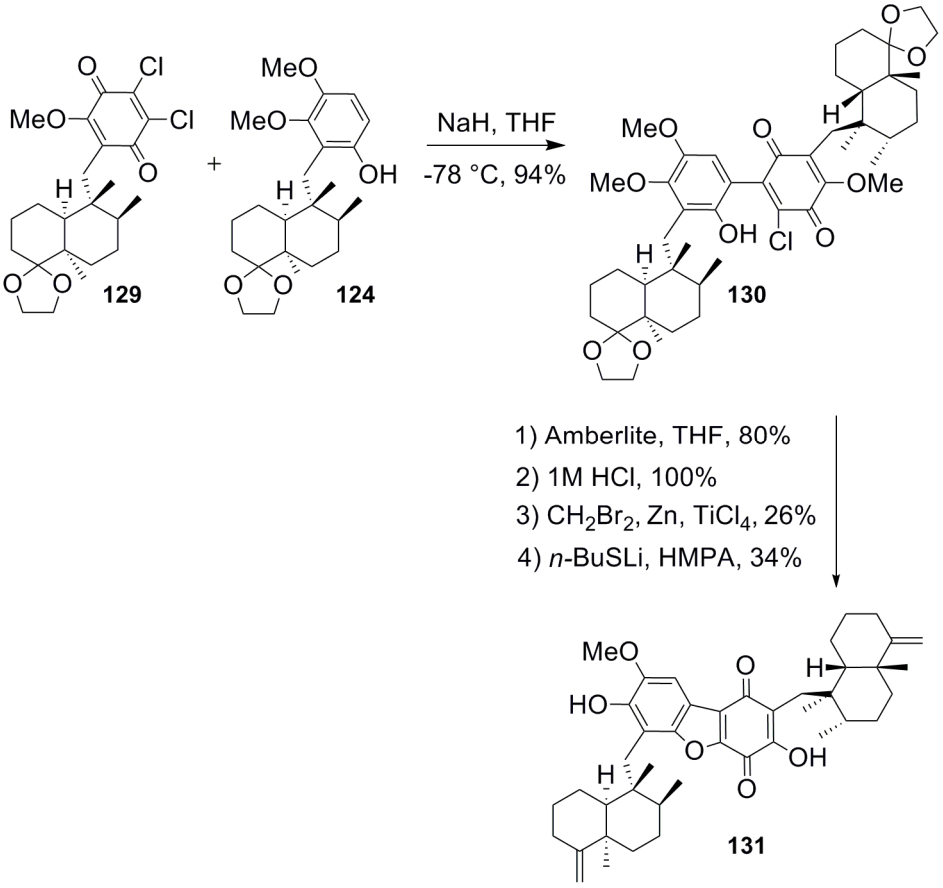
Electrophilic quinone partner **129** was synthesised in a similar manner. Coupling of *cis*-decalin **74** with 1-bromo-2-methoxy-6-(methoxymethoxy)benzene **125** was carried out to afford *neo*-pentyl alcohol **126** in 97%. The resulting alcohol was again converted to the corresponding methyl xanthate, followed by deoxygenation using Barton's conditions to furnish **127**. Acid hydrolysis was performed to remove both the MOM and ketal protecting groups, followed by re-protection of the ketone to give ketal **128** (60% yield over 5 steps). Reaction to form the crucial quinone was performed with molecular oxygen in the presence of salcomine,[69] in 85% yield. Finally, dichlorination was achieved by treatment with thionyl chloride,[70] leading to the desired quinone portion **129** in 78% yield (Scheme 1.41).



Scheme 1.41: Katoh's synthesis of the quinone fragment **129**.

The final annulation was accomplished in a completely regioselective manner *via* the two-step sequence previously developed on a simple model system (see section 1.6). The initial coupling proceeded smoothly to provide **130** as a single regioisomer in 94% yield. This was followed by ring closure performed using Amberlite® to afford the protected tricyclic core in 80% yield. The final steps required removal of the ethylene acetal groups to reveal the diketone before olefination of both carbonyl groups was investigated. This reaction was found to be unsuccessful using Wittig, Peterson or Tebbe's conditions and was best achieved using a combination of dibromomethane, zinc powder and $TiCl_4$, a method demonstrated by Takai,[71] to give the bis-alkene in a poor 26% yield. Finally, global deprotection would furnish the

target, popolohuanone E (**1**). Due to the instability of the *exo*-olefin under acid conditions, a non-acidic alkylthiolate reagent was used to prevent isomerisation of the double bond. Treatment with *n*-butylthiolate,[72] in HMPA removed two of the methyl ethers providing **131** in 34% yield. Unfortunately, the reaction produced none of the fully deprotected product and longer reaction times and/or higher temperatures led to unidentified degradation. The authors attempted deprotection using a variety of conditions, however all attempts were unsuccessful, therefore preventing completion of the total synthesis (Scheme 1.42).

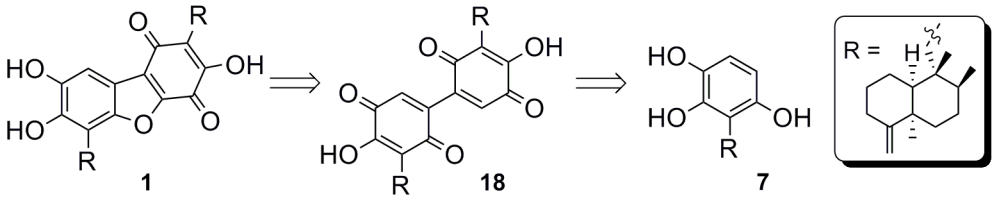


129 **124** **130** **131**

Scheme 1.42: Final steps towards 8-*O*-methylpopolohuanone E (**131**).

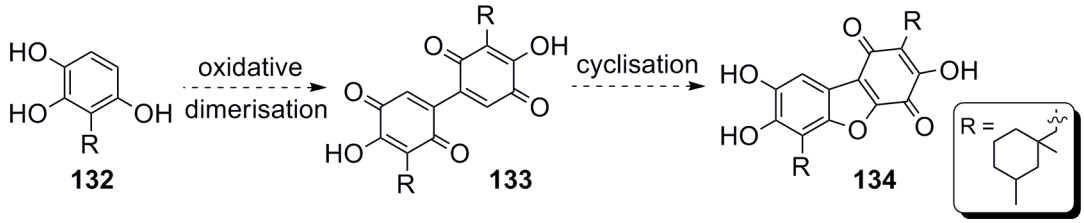
2.0 Proposed Research

This research aimed to complete the total synthesis of the marine natural product, popolohuanone E (**1**). The project aimed to build upon previous studies within the Anderson group,[73] which have focused on the proposed biomimetic route to the central core (Scheme 2.0).



Scheme 2.0: Biomimetic route to the central core.

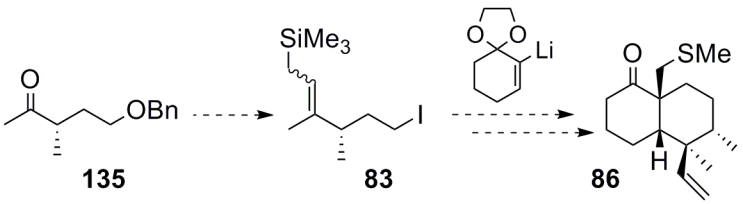
The initial challenge was to carry out an efficient synthesis of model system **132**, therefore allowing investigation into the proposed oxidative dimerisation reaction. Alternative methods for the formation of the desired biaryl bond, including synthesis of the corresponding bis-phenol were also considered (Scheme 2.1).



Scheme 2.1: Model system studies.

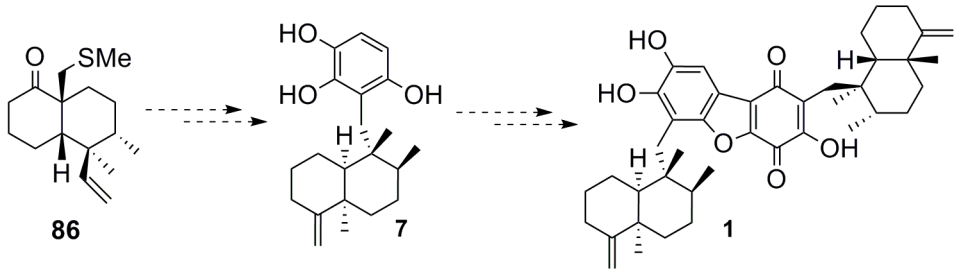
Due to problems with the removal of methyl ether protecting groups within the Anderson group,[73] as well as in Katoh's synthesis,[66] alternative protecting group strategies were required to develop an expedient route to **1**. Therefore, different protecting groups were to be examined, with consideration of the most appropriate removal strategies.

Focus would then turn towards the synthesis of the proposed precursor to **1**, 6'-hydroxyarenarol (**7**), based on the route previously developed within the Anderson group.[73] Synthesis of the enantiopure intermediate iodide **83** would be the initial challenge, with improvements made where possible. With this in hand, iodide **83** would be utilised in the synthesis of the *cis*-decalin core **86**, which has previously been developed using a Hosomi-Sakurai reaction (Scheme 2.2).[74]



Scheme 2.2: Synthesis of *cis*-decalin **86**.

Continuation of the synthesis using *cis*-decalin **86** could then be performed with the aim of synthesising the proposed precursor to **1**, 6'-hydroxyarenarol (**7**). Based on results obtained from the model system studies, oxidative dimerisation on this system would then be explored. Final cyclisation to form the central furan ring would complete the synthesis of popolohuanone E (**1**) (Scheme 2.3).



Scheme 2.3: Final steps towards popolohuanone E (**1**).

3.0 Results and Discussion

The field of natural product synthesis has expanded significantly in recent years.[75] The development of new methodologies and biomimetic strategies has allowed organic chemists to tackle a great variety of densely functionalised, complex molecules, which had previously proved inaccessible. A large quantity of research has focused on developing new synthetic methods based on processes similar to those used in nature. This section describes the work towards a biomimetic total synthesis of the complex secondary metabolite, popolohuanone E (**1**).

3.1 Model System Synthesis

To investigate construction of the dibenzofuran core present in popolohuanone E (**1**), a suitable model system was developed. This system (**132**) had been employed previously within the Anderson group,[76] and it was postulated that further examination would enable the proposed oxidative dimerisation reaction to be investigated. Model **132** contains a number of structural features similar to that found in the proposed precursor to **1**, 6'-hydroxyarenarol (**7**) and was therefore chosen as an appropriate model for these studies (Figure 3.0).

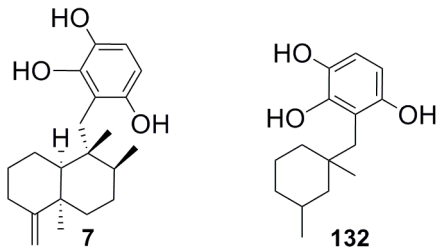
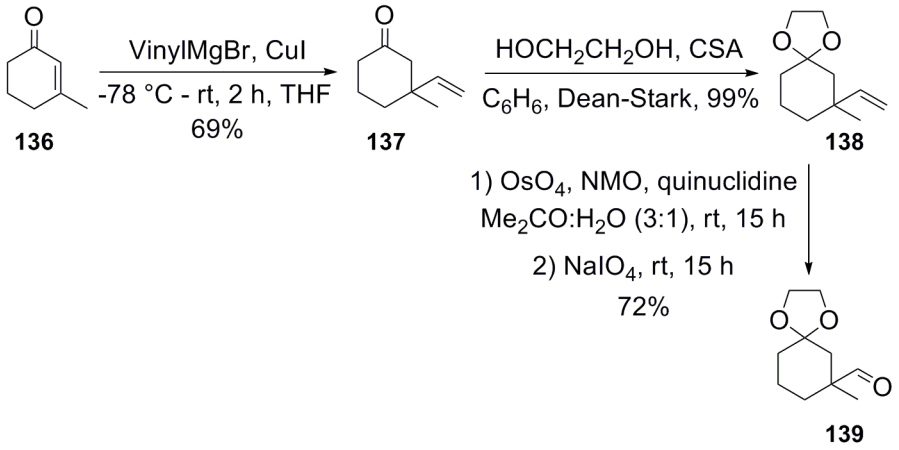


Figure 3.0: Model system **132** representing 6'-hydroxyarenarol (**7**).

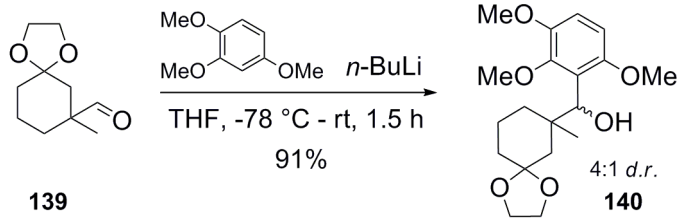
The synthetic strategy for the formation of **132** was based on the route previously developed.[76] Initial studies focused on construction of key intermediate aldehyde **139**. Conjugate addition of vinylmagnesium bromide to methyl-cyclohexenone **136**, using CuI (20 mol%), enabled smooth addition to afford ketone **137** in 69% yield. Subsequent protection using 1,2-dihydroxyethane and CSA under Dean Stark conditions, afforded ketal **138** in 99%. Finally, dihydroxylation of **138** was conducted using Upjohn conditions. Treatment with OsO_4, NMO and quinuclidine, at room temperature for 15 hours, followed by addition of sodium periodate, furnished the desired aldehyde **139** in 72% yield (Scheme 3.0). Attempts to carry out

this final transformation *via* ozonolysis of alkene **138** were also performed, however only traces of the aldehyde were observed when both PPh_3 and DMS were utilised.



Scheme 3.0: Synthesis of aldehyde **139**.

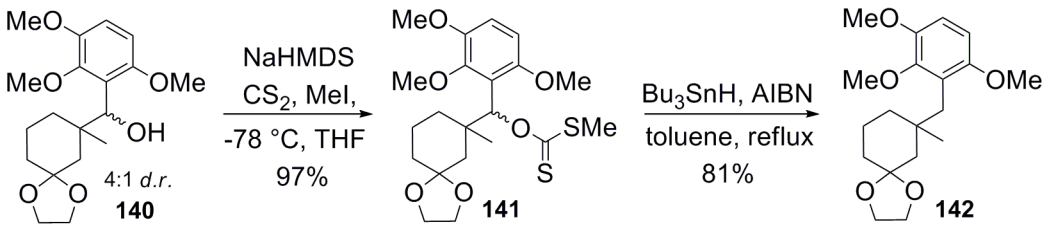
With aldehyde **139** in hand, addition of the phenolic portion was examined. Previous studies had utilised the smooth lithiation of 1,2,4-trimethoxybenzene to carry out this transformation, in the presence of TMEDA. Due to the significant directing effects of the methoxy groups on the aromatic ring, it was postulated that TMEDA could be omitted from the reaction. With this in mind, lithiation of 1,2,4-trimethoxybenzene with *n*-butyllithium followed by addition of aldehyde **139**, successfully afforded alcohol **140** as an inseparable 4:1 mixture of diastereoisomers in 91% yield. Interestingly, the ^{1}H NMR spectra of alcohol **140** showed additional peaks, due to atropisomerism around the Ar-CHOH bond (Scheme 3.1).[77]



Scheme 3.1: Incorporation of phenolic unit.

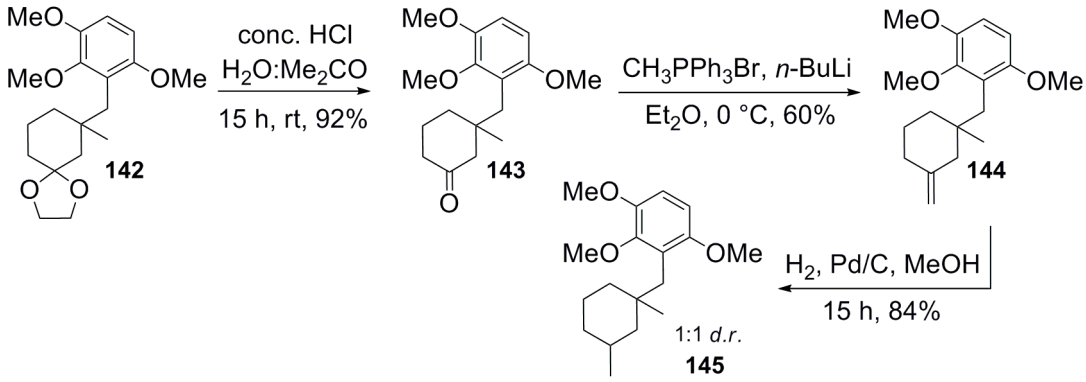
Deoxygenation was then achieved *via* conversion of alcohol **140** to the corresponding xanthate. This methodology was also utilised in Katoh's synthesis of 8-*O*-methylpopolohuanone E (**131**).[78] Deprotonation with NaHMDS, followed by treatment with carbon disulfide and iodomethane gave rise to the corresponding methyl xanthate **141** in 97% yield. The crude material was then subjected to

deoxygenation using conditions developed by Barton and McCombie,[68] to afford deoxygenated product **142** in 81% yield (Scheme 3.2).



Scheme 3.2: Deoxygenation of alcohol **140**.

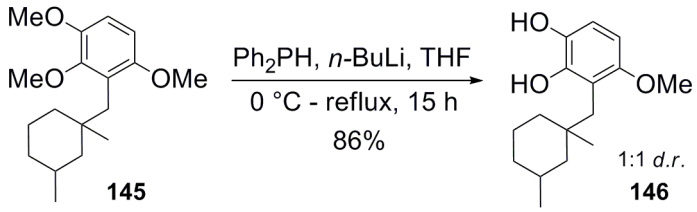
With deoxygenated product **142** in hand, acid hydrolysis of the ketal protecting group was achieved using concentrated HCl in Me_2CO:H_2O (1:1) to give ketone **143** in 92% yield. Subsequent methylenation using *n*-butyllithium and methyl-triphenylphosphonium bromide furnished the corresponding *exo*-cyclic alkene **144** in 60% yield. Due to previous problems with the reactivity of this alkene under oxidative dimerisation conditions (see section 1.0, Scheme 1.35),[79] removal of the alkene was necessary. Treatment of **144** with H_2 and 10% palladium on carbon in MeOH, afforded the desired reduction product **145** in 84% yield as a 1:1 mixture of inseparable diastereoisomers, which was used without further purification (Scheme 3.3). It was found that traces of phosphine impurities, present during the hydrogenation reaction led to prolonged reaction times, therefore additional purification of alkene **144** by column chromatography was required.



Scheme 3.3: Methylenation and hydrogenation.

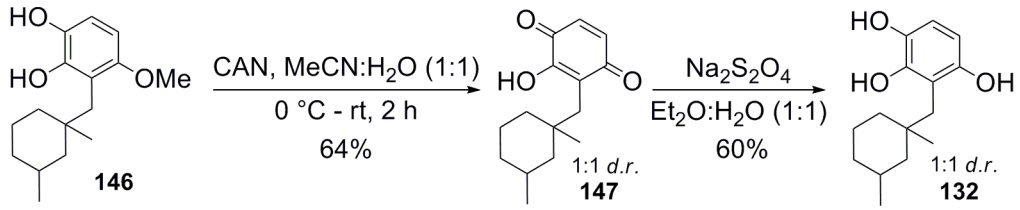
The final challenge in this synthesis involved global deprotection of the methyl ether protecting groups. Unfortunately, demethylation studies carried out in the Anderson group,[79] and by Katoh and co-workers,[66] had experienced extensive problems when using standard demethylation techniques. It was therefore necessary to employ a three-step approach developed previously.[79] Treatment of diphenylphosphine with *n*-

butyllithium (generating $LiPPh_2$ *in situ*) followed by addition of **145** successfully removed two of the three groups, affording the mono-methylated product **146** as a 1:1 mixture of diastereoisomers, in excellent 86% yield (Scheme 3.4). It was found that anhydrous conditions were particularly important for the removal of both methyl groups, with single de-methylation occurring in some cases.



Scheme 3.4: Demethylation using diphenylphosphine.

Finally, deprotection of the remaining methyl ether was carried out according to conditions developed by Weimer and Scott, in their synthesis of arenarol (**2**).[80] Subjecting **146** to oxidative conditions using ceric ammonium nitrate (CAN) afforded the corresponding *p*-quinone **147** as a 1:1 mixture of diastereoisomers, in 64% yield. Reduction to the required phenol using sodium dithionite then afforded **132** in 60% yield (again as a 1:1 mixture of diastereoisomers), providing the desired model system structure (Scheme 3.5).



Scheme 3.5: Final steps towards model system **132**.

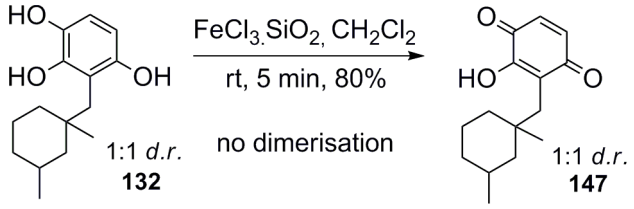
Although the deprotection route proved relatively low yielding (33% over 3 steps), this methodology successfully provided a viable route to the desired phenolic compound. The model system synthesis was accomplished in 12 steps, in a moderate 3.1% overall yield. With the synthesis of phenol **132** completed, investigations into the proposed oxidative dimerisation studies could be conducted.

3.2 Dimerisation Studies

Previous investigations towards the synthesis of popolohuanone E (**1**) have provided valuable knowledge of the behaviour of the phenolic systems involved in the proposed synthesis (see section 1.2). With this information available, the first challenge was to utilise phenol **132** to explore the proposed oxidative dimerisation

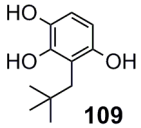
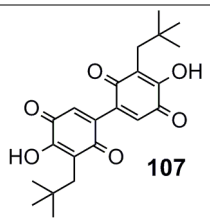
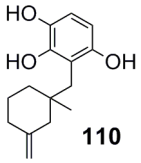
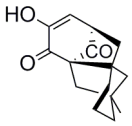
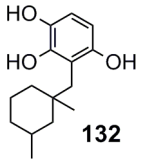
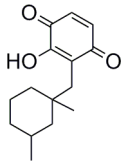
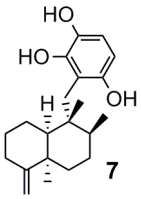
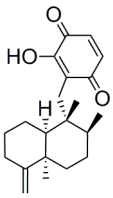
reaction. If successful, findings from this study could be applied to the proposed precursor to **1**, 6'-hydroxyarenarol (**7**).

Initial attempts to induce oxidative dimerisation were conducted using conditions developed for a similar phenolic compound **109** (see section 1.5 and Table 3.0).[81] Phenol **132** was subjected to $FeCl_3.SiO_2$ (8 equivalents) in CH_2Cl_2 for five minutes, before being filtered and concentrated. Unfortunately, only oxidation to the corresponding mono-quinone **147** was observed in 80% yield, with no evidence of any dimerisation products (Scheme 3.6).



Scheme 3.6: Initial dimerisation reaction.

This result indicated that although the phenolic systems studied during this research and in previous work within the Anderson group, were very similar in structure, each system demonstrated very different reactivity under the oxidative dimerisation conditions (Table 3.0). When phenol **109**, bearing a simple tertiary butyl group was employed, dimerisation was performed successfully in an excellent 81% yield (Table 3.0, Entry 1). However, when incorporating the *exo*-cyclic alkene in the system (**110**) subjection to the same conditions led to an intramolecular [5+2] cycloaddition product **111** (Table 3.0, Entry 2).[79] When using the new model system **132**, (with this alkene removed), no intramolecular reactions were seen, however only mono-quinone **147** was recovered (Table 3.0, Entry 3). This was also the case when the same conditions were applied to 6'-hydroxyarenarol (**7**), affording the corresponding mono-quinone **112** (Table 3.0, Entry 4).[79]

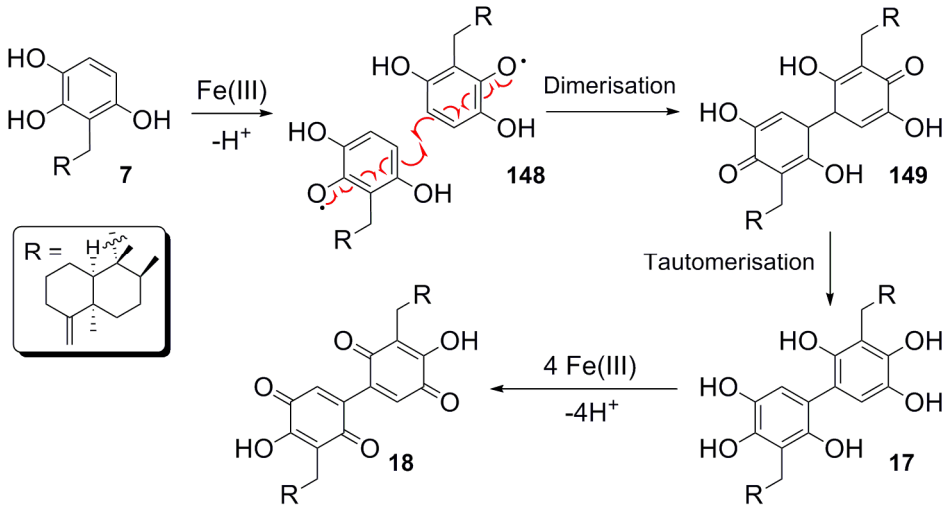
Entry	Phenol	Result[a]
1	 **109**	 **107**
2	 **110**	 **111**
3	 **132**	 **147**
4	 **7**	 **112**

[a] Phenol treated with 8 equivalents of $FeCl_3.SiO_2$ in CH_2Cl_2, 5 min, rt.

Table 3.0: Structural comparisons of phenolic systems.

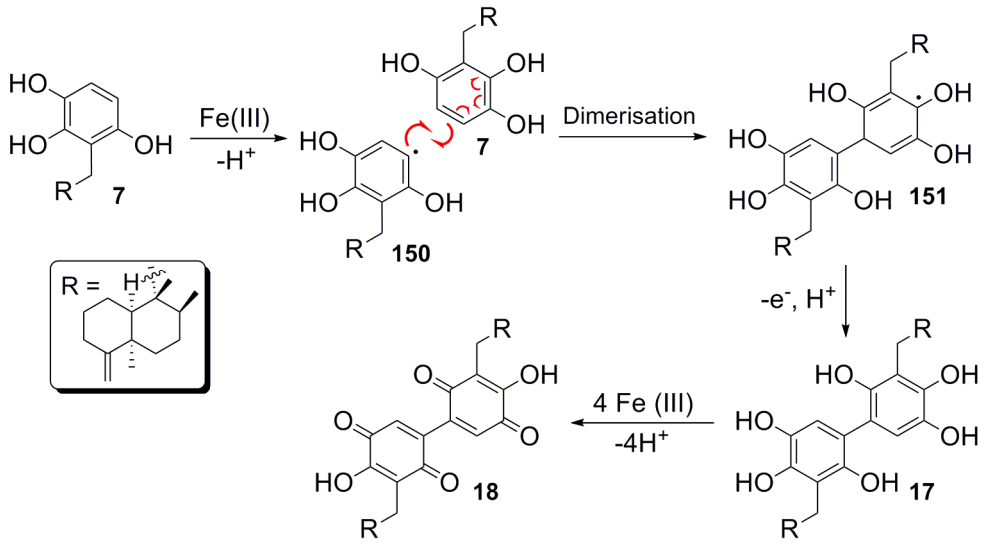
Due to the results described above, further investigation was required to examine the cause of the differing observed reactivity. It was also necessary to develop robust dimerisation conditions that would allow the proposed coupling to be carried out on both the model system (**132**) and the 'real' or 6'-hydroxyarenarol system (**7**). Initial studies continued to focus on the use of $FeCl_3.SiO_2$, which is advantageous due to the ease with which it can be removed from the reaction mixture. In addition, when using $FeCl_3$ without a solid support it has been reported that the inorganic material was difficult to separate from the organic mixture.[79] To examine this reaction fully, a more detailed investigation of the mechanism was required. Previous work has suggested a radical process for the dimerisation reaction,[76] requiring 8 equivalents of $FeCl_3.SiO_2$ (Scheme 3.7). Two molecules of the required phenol **7** could undergo electron transfer to afford Fe(II) and the corresponding phenol radical cations. Subsequent proton loss could afford two radical species **148**, which could undergo dimerisation to afford intermediate **149**. Tautomerisation would furnish the

corresponding bis-phenol **17**, which upon further oxidation, would yield the desired bis-quinone **18**. In addition to its use as a single electron transfer reagent, it is known that $FeCl_3$ can act as a Lewis acid, which could activate the phenol molecules and assist the dimerisation process. It is also postulated that $FeCl_3$ could have a chelating effect under the reaction conditions, which could bring the phenol molecules into close proximity and hence promote the dimerisation reaction.



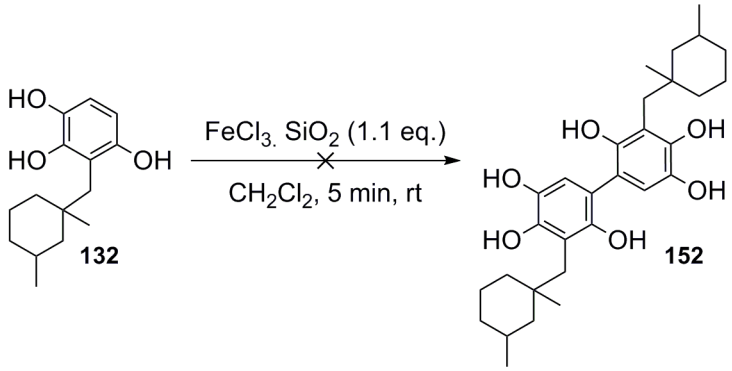
Scheme 3.7: Mechanism of oxidative dimerisation.

Alternatively, it has been suggested in the literature (see section 1.4), that the dimerisation mechanism could proceed *via* electron transfer of one phenol molecule (**7**) followed by proton loss to afford the corresponding radical species **150**. This could then undergo further reaction with a neutral molecule (**7**) to afford radical species **151**. Loss of an electron and rearomatisation could give biaryl **17**, which upon oxidation, could furnish the desired bis-quinone **18** (Scheme 3.8). Both of the proposed dimerisation mechanisms are suggested to proceed *via* a radical cation species and hence the intermediate bis-phenol **17**. Therefore, it was suggested that although it would be difficult to determine which pathway was occurring under the reaction conditions, the use of $FeCl_3$ could enable either of these routes to proceed, therefore studies were continued as planned.



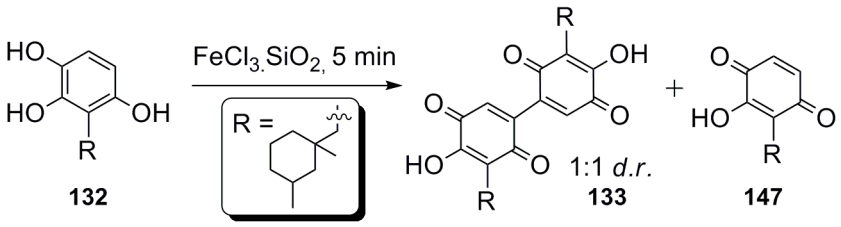
Scheme 3.8: Alternative oxidative dimerisation mechanism.

The proposed mechanisms for dimerisation suggest that when conducting oxidative dimerisation of model **132**, the corresponding bis-phenol **152** could be formed under the reaction conditions. It was therefore postulated that using less equivalents of iron(III) chloride might enable isolation of this important intermediate. In addition, examples in the literature have made use of one equivalent of $FeCl_3$ in the presence of air to obtain similar phenolic compounds (see section 1.4). If isolation of **152** could be possible, further oxidation by treatment with excess $FeCl_3$ could enable formation of the desired bis-quinone **133**. With this in mind, treatment of phenol **132** with 1.2 equivalents of $FeCl_3.SiO_2$ in CH_2Cl_2 was carried out under the previously used conditions. Analysis by TLC showed complete consumption of starting material, therefore an additional 8 equivalents of $FeCl_3$ was added to allow further oxidation. Unfortunately, isolation of the reaction mixture afforded only the corresponding mono-quinone **147** (Scheme 3.9).



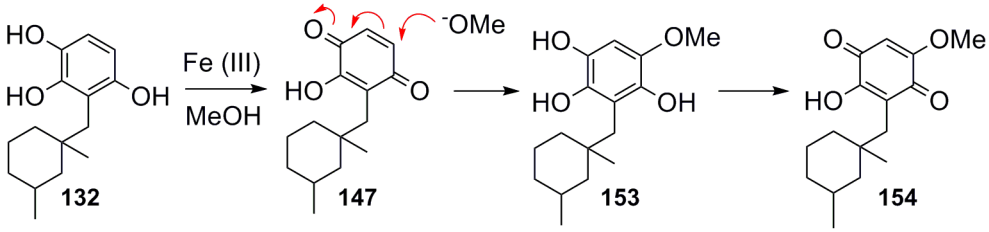
Scheme 3.9: Attempted formation of bis-phenol **152**.

Due to the inability to form the corresponding bis-phenol **152** or bis-quinone **133** using these conditions, focus turned to variation of the reaction conditions. This began with a screen of alternative solvents for the biaryl reaction (Table 3.1). Conducting the reaction in CH_2Cl_2 or a 1:1 mixture of CH_2Cl_2 and MeCN afforded only the mono-oxidation product **147** both in 80% yield (Table 3.1, Entry 1-2). However, when changing the solvent to methanol, traces of the desired bis-quinone were observed as well as by-product **154** in 15% yield, which had not been observed in previous work (Table 3.1, Entry 3). It is presumed that **154** is formed by oxidation of **132** to the corresponding quinone **147**, followed by conjugate addition of a methoxy anion and rearomatisation to give phenol **153**. This could then undergo further oxidation under the reaction conditions to give the observed product **154** (Scheme 3.10). With this result in mind, it was postulated that use of a less nucleophilic, protic solvent could be beneficial. It was suggested that the use of H_2O as a reaction solvent could fit this criteria. Use of a 9:1 H_2O:MeOH solvent system (methanol was necessary to dissolve the substrate) delightfully afforded the desired bis-quinone in 35% yield with 50% of the corresponding mono-quinone (Table 3.1, Entry 4). With this pleasing result, it was suggested that different alcohols could have an effect on the reaction conditions, therefore a H_2O:*t*-BuOH (9:1) solvent system was employed. Unfortunately this gave a similar result, with less recovery of mono-quinone (Table 3.1, Entry 5). Finally the reaction was performed using H_2O:THF, H_2O:CH_2Cl_2 and H_2O:Me_2CO mixtures, which unfortunately led to similar yields of the bis-quinone **133** and mono-quinone **147** (Table 3.1, Entries 6-8).



Entry	Solvent(s)	Yield 133 (%)	Yield 147 (%)
1	CH_2Cl_2	-	80
2	CH_2Cl_2:MeCN	-	80
3	MeOH	trace	**154** (15%)
4	H_2O:MeOH (9:1)	35	50
5	H_2O:*t*-BuOH (9:1)	39	33
6	H_2O:THF (9:1)	0	29
7	H_2O:CH_2Cl_2 (9:1)	30	28
8	H_2O:Me_2CO (9:1)	40	19

Table 3.1: Variation of the reaction solvent.



Scheme 3.10: Possible formation of by-product **154**.

This study had developed conditions in which the desired phenolic coupling reaction could be carried out effectively. Despite the low yield of this reaction, recovery of significant amounts of the mono-quinone **147** was achieved, which could be recycled by reduction to the phenol **132** using $Na_2S_2O_4$. With this result in hand, focus was turned towards manipulation of the remaining reaction parameters.

During these studies, it was observed that the reaction mixture turned from yellow to dark brown immediately after addition of phenol **132**. In addition, complete consumption of starting material was observed when the reaction mixture was analysed after just five minutes at room temperature. These factors indicated that the

reaction was proceeding rapidly and it was therefore suggested that portionwise addition of the substrate could lead to a higher yield of the bis-quinone **133**. Phenol **132** was dissolved in Me_2CO and added dropwise to a slurry of $FeCl_3.SiO_2$ in H_2O. Unfortunately, this again led to a poor yield of 16% of the bis-quinone with 47% of the corresponding mono-quinone **147** (Table 3.2, Entry 1). It was also postulated that the concentration of the reaction could have an effect on reactivity, therefore performing the reaction at high concentration could force the phenol molecules into close proximity and hence promote dimerisation. Phenol **132** in Me_2CO was added to a small column of $FeCl_3.SiO_2$ (loaded in H_2O:Me_2CO, 9:1). Unfortunately, this also led to poor yield of the bis-quinone (14%) (Table 3.2, Entry 2). Conversely, using dilute conditions (four times the amount of solvent used previously) also led to a low yield of the bis-quinone **133** (Table 3.2, Entry 3). These results suggest that despite changes in the reaction conditions, oxidation of phenols of this type, by Fe(III) is particularly efficient. With this in mind, alternative strategies were investigated.

Entry	Conditions	Yield 133 (%)	Yield 147 (%)
1	portionwise[a]	16	47
2	concentrated[b]	14	48
3	dilute[c]	23	40

[a] Portionwise addition of phenol **132** in Me_2CO to a slurry of $FeCl_3.SiO_2$ in H_2O.

[b] Phenol dissolved in minimum amount of acetone and pushed through column of $FeCl_3.SiO_2$.

[c] Four times the normal amount of solvents used.

Table 3.2: Variation of reaction parameters.

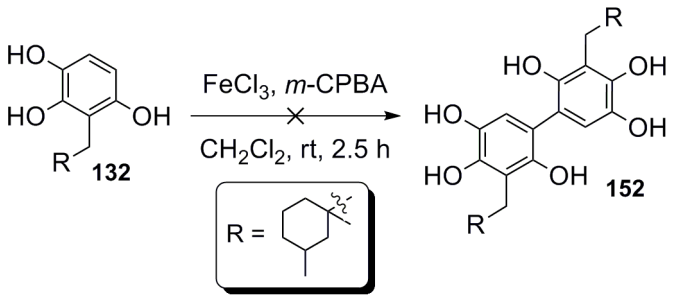
Although conditions for the formation of the bis-quinone **133** had now been developed, improvement in the yield would be required for the reaction to be utilised in this synthesis, as well as other biaryl bond forming applications. For this reason, alternative methods for the coupling reaction were explored. It was postulated that a study of the oxidation potential of the phenolic substrate **132** and possible oxidising reagents could help our understanding of the oxidative processes occurring under the reaction conditions. It was proposed that the ideal reagent would have a reduction potential marginally above the oxidation potential of the substrate, allowing oxidation to occur at a slower rate which could also decrease the rate of rapid oxidation to the mono-quinone **147**. It was also considered that mono-quinone **147** formed in the

reaction could itself act as an oxidising agent, promoting formation of mono-quinone **147** over the bis-quinone **133**. Potentials for both the phenol **132** and mono-quinone **147** were measured and compared to known potentials for common oxidative reagents.[82] Values are quoted relative to the standard hydrogen electrode.

Reduction potential of phenol **132**	=	- 0.70 V
Reduction potential of mono-quinone **147**	=	+ 0.45 V
Reduction potential of Fe^{3+}	=	+ 0.77 V
Reduction potential of CAN	=	+ 1.44 V
Reduction potential of chloranil	=	+ 0.70 V
Reduction potential of DDQ	=	+ 1.00 V
Reduction potential of 1,4-benzoquinone	=	+ 0.72 V

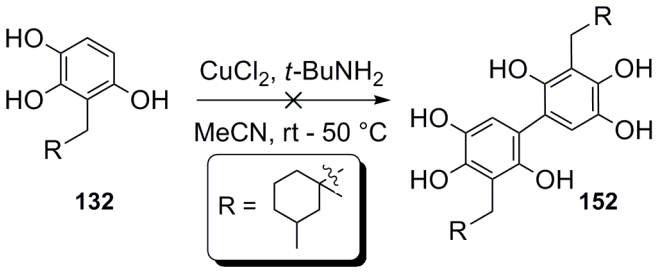
The results indicated that $FeCl_3$ is a good candidate for the oxidation of our substrate, with the potential for the Fe(III)/Fe(II) process being higher than that for phenol **132**. In addition, the reduction potential for quinone **147** (+0.45) is also higher than the potential for the phenol **132**, indicating that any quinone **147** formed in the reaction, could also be involved in oxidation of the phenolic substrate. The information gained in this study would aid the choice of oxidising agents when investigating alternative strategies to the biaryl bond forming reaction.

During this research program, Wang *et al.* published an intermolecular Fe(III) chloride catalysed coupling of phenolic compounds, using *m*-CPBA as an oxidant (see section 1.4).[40] It was suggested that this methodology could be applied to the phenolic system **132** required for the proposed biomimetic synthesis. Subjecting phenol **132** to the oxidative conditions using *m*-CPBA (10 mol%) in CH_2Cl_2, unfortunately led to un-reacted starting material being recovered, with some degradation. Despite the oxidative coupling being unsuccessful in this case, the substrates used by Wang were protected as the corresponding methyl ethers, which may be imperative for the success of this catalytic reaction (Scheme 3.11).



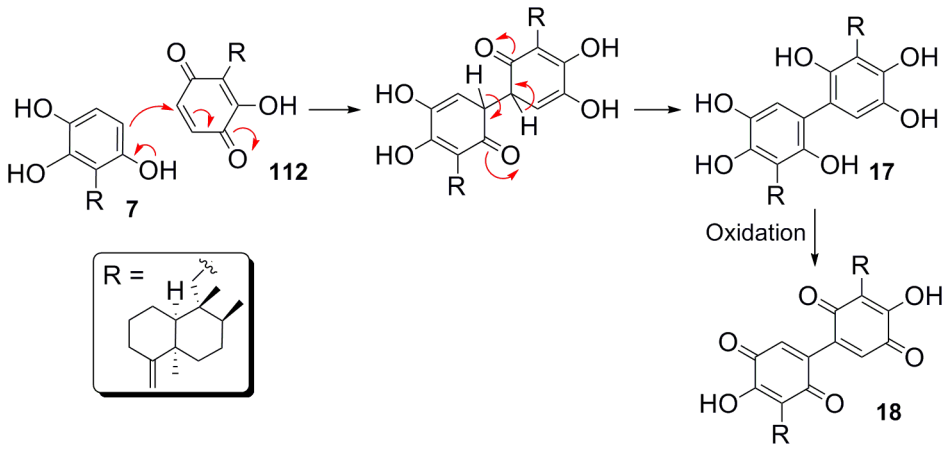
Scheme 3.11: Attempted $FeCl_3$/*m*-CPBA catalysed oxidative coupling.

In addition to the use of $FeCl_3$, a number of alternative methods for couplings of this type are described in the literature. Yamamoto *et al.* has reported the coupling of naphthol derivatives using a 1,2-diphenylethylamine-copper(II) complex.[83] This methodology was subsequently developed further using the complex formed *in situ* from $CuCl_2$ (4 equivalents) and *t*-butylamine (16 equivalents).[84] With this in mind, phenol **132** was subjected to the reported conditions using MeCN. Analysis of the reaction mixture by TLC showed no conversion after two hours at room temperature and unfortunately, only degradation of the starting material was seen when the mixture was heated to 50 °C (Scheme 3.12). Reports in the literature also achieved successful results using methanol as the solvent,[85] however it was thought that this may lead to unwanted side products as seen previously in the $FeCl_3.SiO_2$ case (Scheme 3.12).



Scheme 3.12: Attempted coupling with $CuCl_2$/*t*-$BuNH_2$ complex.

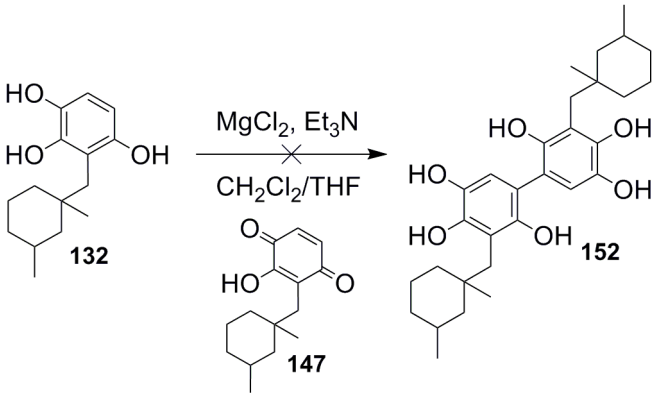
In addition to the mechanistic pathways for oxidative coupling described above (Scheme 3.7 and 3.8), an alternative route was also considered. It is known that *p*-quinones are particularly susceptible to conjugate addition reactions.[86] It was therefore postulated that under the correct conditions, the biaryl bond required for this synthesis could be formed by conjugate addition of 6'-hydroxyarenarol (**7**) to the corresponding quinone **112**. After tautomersation, this could afford the bis-phenol **17**, which upon oxidation, would furnish the desired bis-quinone **18** (Scheme 3.13).



Scheme 3.13: Alternative mechanism for biaryl coupling.

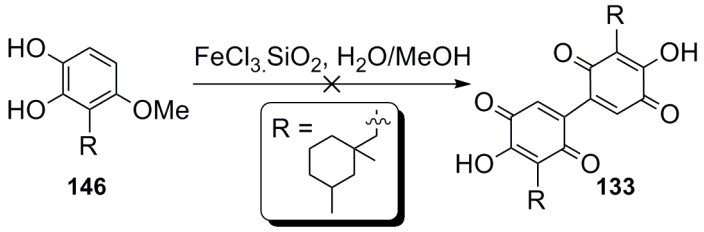
During studies towards the synthesis of **1**, Katoh *et al*. also considered this approach.[56] This work demonstrated that an unactivated quinone such as **147** would not undergo the proposed reaction, however if a chloro-substituted quinone was utilised, the conjugate addition proceeded smoothly. This approach was subsequently used in the synthesis of 8-*O*-methylpopolohuanone E (**131**) (see section 1.7).[78] Despite this report, it was postulated that activation of the quinone *via* an alternative method could be possible.

A search of the literature led to the suggestion that the reaction could be promoted by a bifunctional catalyst system, pioneered by Shibasaki.[87] This process would allow the use of both Lewis acid and Brønsted base catalysis, to activate both molecules towards reaction. Complimentary to this, reports in the literature have described the coupling of phenols using Et_3N and $MgCl_2$, in the synthesis of salicylnitriles.[88] With this in mind, treatment of phenol **132** with $MgCl_2$, triethylamine and quinone **147** in CH_2Cl_2 showed disappearance of starting material to a purple spot. Isolation was carried out only to reveal the starting material phenol **132**, suggesting that the substrate had been deprotonated, however no further reaction had occurred. When using THF as the solvent, no further reaction was seen and when the mixture was heated to reflux the material appeared to degrade (Scheme 3.14).



Scheme 3.14: Attempted biaryl bond formation with $MgCl_2/Et_3N$ system.

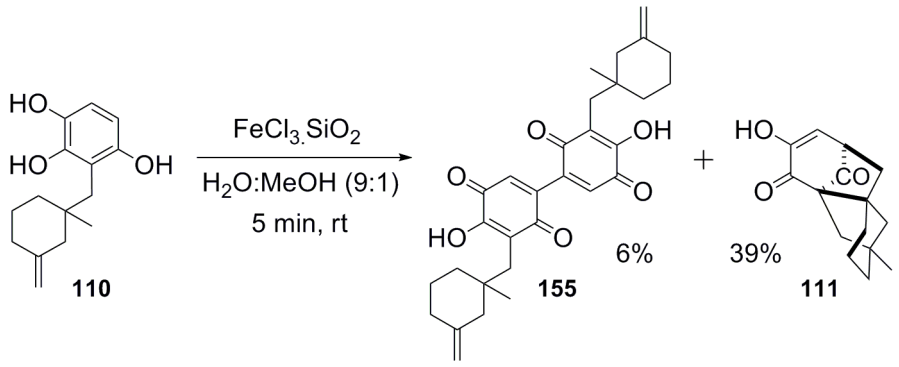
Many examples in the literature have also demonstrated the oxidative coupling of protected phenols (see section 1.4). It was proposed that performing the oxidative dimerisation with mono-protected phenol **146** might enable dimerisation to either the bisphenol **152** or bis quinone **133**. Phenol **146** was treated with 8 equivalents of $FeCl_3.SiO_2$ in H_2O:MeOH (9:1) at 0 °C for 5 minutes followed by warming to room temperature. Unfortunately, analysis of the crude material demonstrated only a complex mixture of degradation products (Scheme 3.15).



Scheme 3.15: Attempted dimerisation of protected phenol **146**.

Although studies to improve the yield of the coupling reaction were largely unsuccessful, new conditions for the dimerisation on this system had been developed. With these results in hand, application of these conditions to a phenolic system bearing the *exo*-cyclic alkene was necessary. Using the optimised conditions, phenol **110** was subjected to 8 equivalents of $FeCl_3.SiO_2$ in H_2O:MeOH (9:1) for 5 minutes, which led to a large amount (39%) of the [5+2] cycloaddition product **111**. However, a small amount (6%) of the desired bis-quinone **155** was also seen (Scheme 3.16). This was a very positive result, as dimerisation was not observed during previous studies on this system. This encouraging result also indicated that the reaction conditions could later be applied to the 'real' or 6'-hydroxyarenarol (**7**) system. With alkene **110** available, the reaction was also attempted using brine in place of H_2O as a solvent. It was suggested that the increased ionic nature would promote coordination

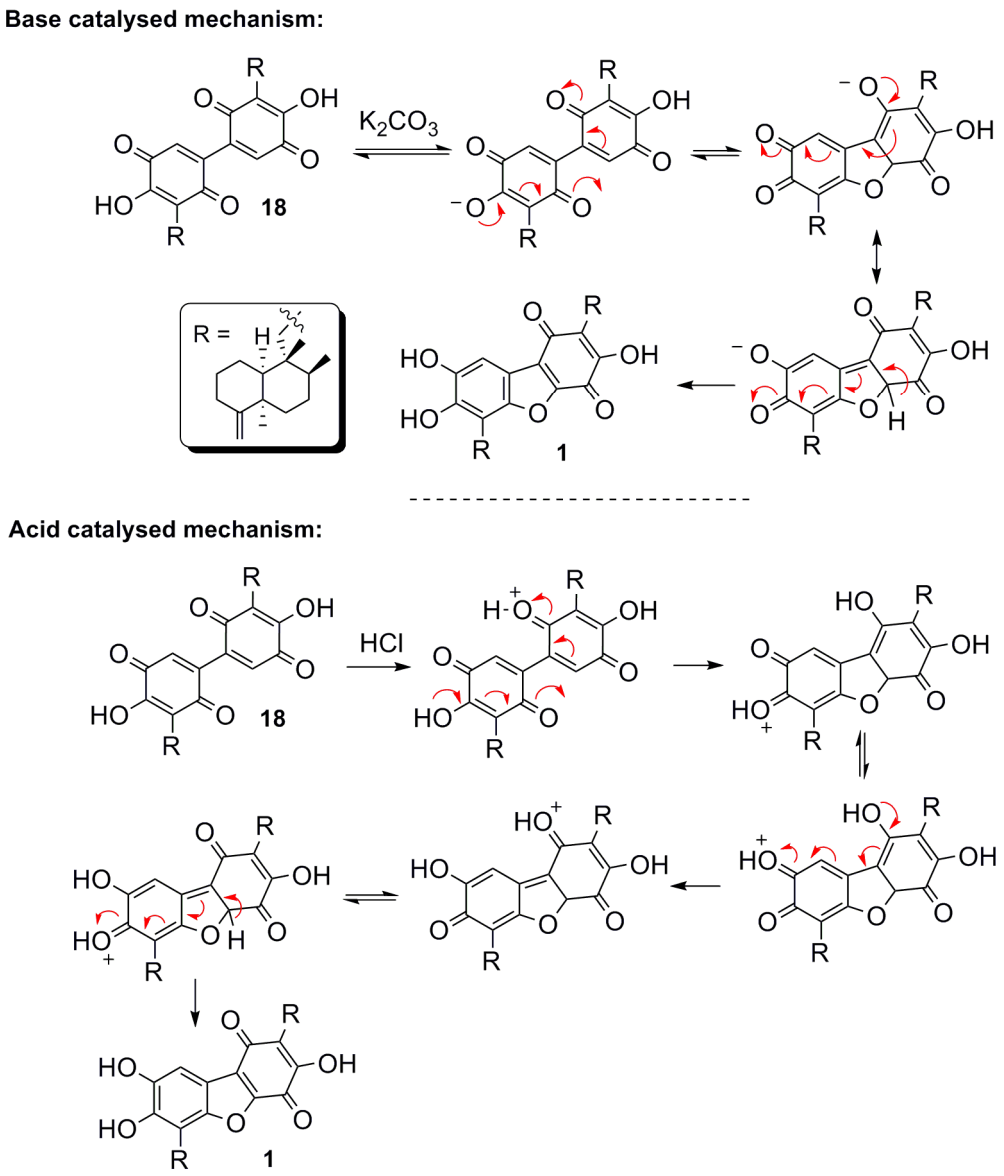
of Fe(III) to phenol **110** and hence encourage dimerisation. These conditions afforded a slight increase in the bis-quinone **155** to 10% yield, with 50% of the corresponding [5+2] cycloaddition product **111**. The large yield of **111** produced in these reactions was not a concern, as previous work had also shown that the intramolecular [5+2] cycloaddition was not seen when subjecting 6'-hydroxyarenarol (**7**) to the oxidative conditions. It was suggested that this was due to the reactive *exo*-cyclic alkene being much further away from the aromatic portion of the molecule, compared with that in model system **110**. Therefore it was postulated that under the new conditions, dimerisation of the proposed precursor to popolohuanone E (**1**) would be possible.



Scheme 3.16: Oxidative dimerisation using alkene system **110**.

3.3 Studies Towards the Central Core

With bis-quinone **133** in hand, the final challenge for this model system was to construct the central furan ring and hence furnish the tricyclic core found in popolohuanone E (**1**). Previous studies within the Anderson group,[76] as well as reports in the literature (see section 1.6) had led to the proposal that cyclisation could proceed *via* an acid or base catalysed process to form the central core (Scheme 3.17).



Scheme 3.17: Mechanistic proposals for cyclisation.

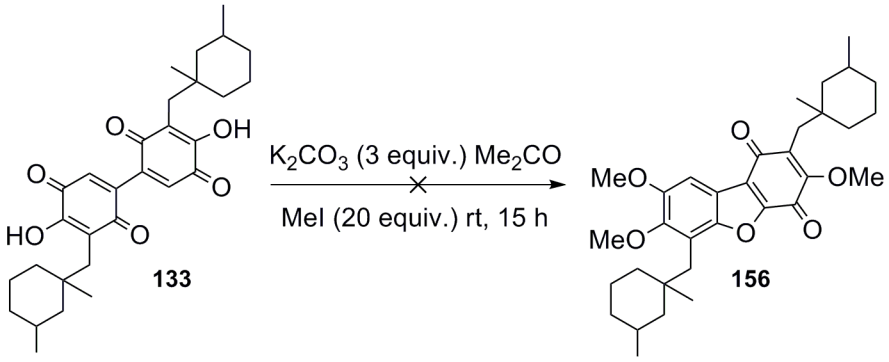
With these mechanisms in mind, studies initially focused on the base catalysed method. Based on previous studies,[76] treatment of bis-quinone **133** with three equivalents of K_2CO_3 in Me_2CO for 15 hours at room temperature showed no sign of the desired product and a complex mixture of starting material, as well as a number of brightly coloured unidentifiable products were isolated (Table 3.3, Entry 1). It was postulated that these products could resemble the proposed intermediates in the reaction pathway and that more forcing conditions could enable the reaction to reach completion. Unfortunately, increasing the number of equivalents of K_2CO_3 produced the same outcome (Table 3.3, Entry 2). In addition, increasing the time of the reaction was found to lead to degradation of the starting material (Table 3.3, Entry 3)

and heating to reflux for 15 hours led to the same result (Table 3.3, Entry 4). Finally, performing the reaction at 0 °C showed no reaction by TLC analysis, therefore the reaction was warmed to room temperature, however again this afforded a complex mixture of products (Table 3.3, Entry 5).

Entry	Equiv. K_2CO_3	Conditions	Result
1	3	15 h, rt	complex mixture
2	6	15 h, rt	complex mixture
3	6	96 h, rt	degradation
4	3	15 h, reflux	degradation
5	3	15 h, 0 °C - rt	complex mixture

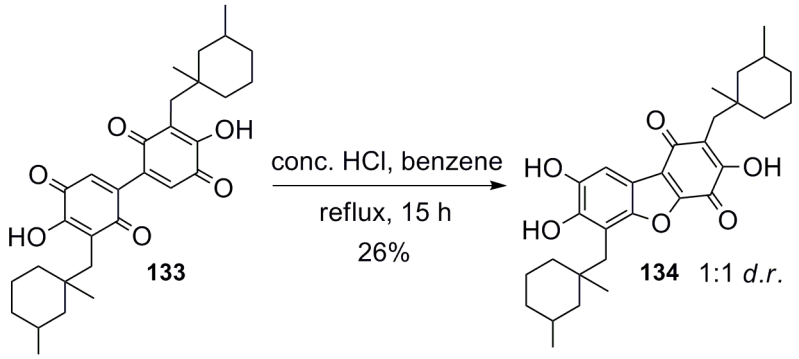
Table 3.3: Cyclisation conditions towards the tricyclic core.

These results indicated that the presence of a more lipophilic group on this system (**133**), when compared to the previously used bis-quinone (**107**) was preventing cyclisation and hence isolation of the desired tricyclic core. In addition to the direct cyclisation to form the dibenzofuran core, previous work had demonstrated the formation of a number of protected analogues of the central core.[76] Due to the difficulties in constructing the required tricycle, it was postulated that addition of a suitable electrophile could improve the stability of the dibenzofuran structure and allow isolation of the protected tricyclic core on this system. Treatment of bis-quinone **133** with K_2CO_3, followed by addition of MeI led to disappearance of starting material by TLC analysis and a number of brightly coloured spots were observed. Unfortunately, upon isolation, analysis of the material indicated a complex mixture of products (Scheme 3.18). With these disappointing results, attention was turned to the acid catalysed strategy.



Scheme 3.18: Attempted isolation of protected tricyclic core.

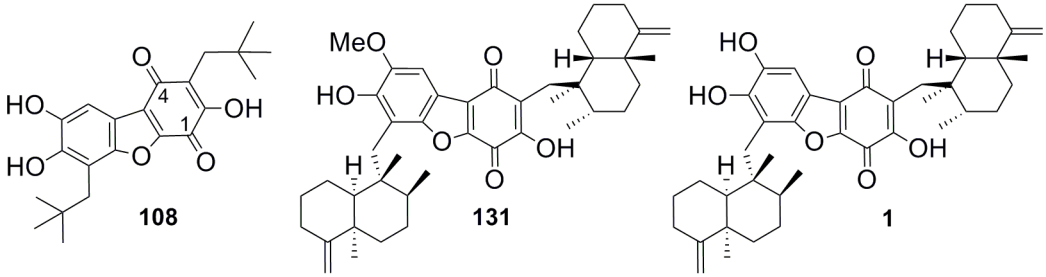
With the base catalysed method proving unsuccessful, the reaction was attempted using acid catalysis. Treatment of bis-quinone **133** with two drops of concentrated HCl in benzene, followed by heating to reflux for 15 hours, led to successful formation of the dibenzofuran structure **134** as a 1:1 mixture of diastereoisomers in 26% yield, as a dark purple solid (Scheme 3.19). The remainder of the material appeared to consist of only degradation products.



Scheme 3.19: Successful formation of the dibenzofuran tricyclic core.

Further attempts to increase the efficiency of this reaction by prolonging the reaction time (36 hours), provided no increase in yield. Increasing the quantity of acid was not attempted at this time, as it was postulated that this could enhance the amount of degradation observed. Purification of the crude material by flash column chromatography also proved difficult, due to degradation whilst on silica, however it is known that previous studies had also encountered problems with isolation of similar compounds.[76] It was therefore suggested that the low yield could be attributed to difficulties with isolation and purification as well as degradation during the reaction. With more time, a screen of suitable acid and base catalysts could be performed to improve the yield of this reaction. With the tricyclic structure successfully constructed, data for **134** was compared with that obtained for previously

synthesised model system (**108**),[76] Katoh's 8-*O*-methylpopolohuanone E (**131**),[66] and popolohuanone E (**1**) showing excellent correlation between each compound (Table 3.4).



Entry	Compound	δ C=O (1) ppm	δ C=O (4) ppm
1	**134**[a]	170.6	185.6
2	**108**[b]	171.9	185.5
3	**131**[c]	170.8	185.0
4	**1**[c]	170.8	185.4

[a] Sample obtained in $CDCl_3$. [b] Sample obtained in $(CD_3)_2SO$. [c] Sample obtained in CD_2Cl_2.

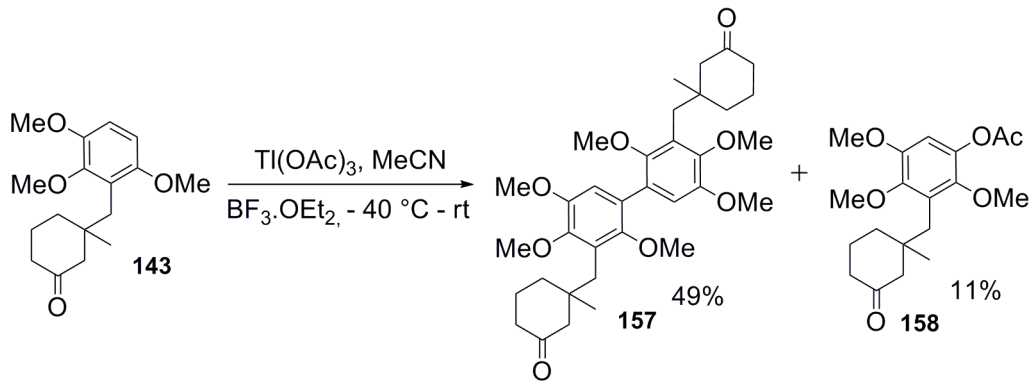
Table 3.4: ^{13}C NMR comparison of known tricyclic core data.

The successful formation of the tricyclic core had concluded the biomimetic synthesis on this model system. Development of new dimerisation conditions, as well as formation of the tricyclic core on this system, indicated that this pathway could be utilised when constructing the core using 6'-hydroxyarenarol (**7**). These results provided strong evidence that popolohuanone E (**1**) could be synthesised *via* this biomimetic route.

3.4 Alternative Pathways to the Central Core

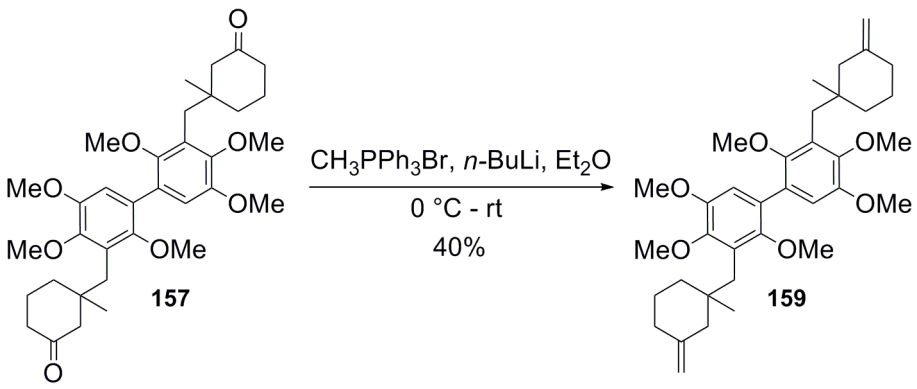
In addition to the biomimetic pathway described previously, alternative methods for formation of the desired biaryl bond were examined. Methodology concerning biaryl couplings of this type are now widely reported in the literature (see section 1.4), and involve a large variety of metal catalysed reactions. Many of these require coupling of two different partners, using a halo- or *pseudo* halogenated compound, however, for the purposes of an efficient strategy towards popolohuanone E (**1**), the investigation remained focussed on the coupling of two identical partners.

Successful dimerisations of this nature have been reported using thallium(III) compounds.[89] To this end, coupling of intermediate **143** using thallium(III) acetate was attempted. Treatment of a degassed solution of ketone **143** in MeCN with a solution of $Tl(OAc)_3$ in MeCN (also degassed) followed by addition of $BF_3.OEt_2$, afforded the desired biaryl product **157** in moderate 49% yield. An additional 11% of the oxidative substitution by-product **158** was also seen (Scheme 3.20).



Scheme 3.20: Thallium(III) promoted biaryl coupling.

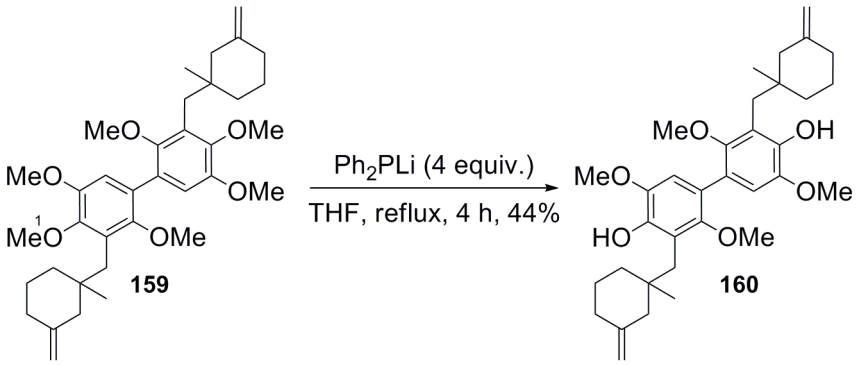
With coupling to form biaryl **157** proving achievable, bis-methylenation was investigated to install the desired *exo*-cyclic alkene functionality. During studies on the model system (see section 3.1), a simple Wittig reaction was successfully conducted to install this alkene functionality, therefore it was suggested that these conditions could also be suitable for the synthesis of the corresponding dimer **159**. Methylenation of bis-ketone **157** was performed using *n*-butyllithium and methyltriphenylphosphonium bromide to afford the corresponding bis-alkene **159** in 40% yield (Scheme 3.21). Although this transformation was relatively low yielding, Katoh *et al*.[66] had also reported poor yields when performing bis-methylenation on a similar biaryl, suggesting that this process is particularly difficult on these systems.



Scheme 3.21: Wittig reaction to form bis-alkene **159**.

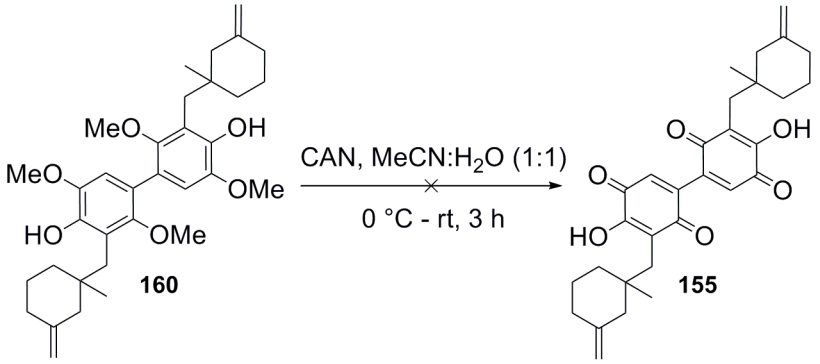
With bis-alkene **159** available, completion of the tricyclic core *via* this route required deprotection of six methyl ether groups. If this was possible, oxidation of the resulting phenol could lead to bis-quinone **133** and coincide with the previously described biomimetic synthesis (see section 1.2). Final acid catalysed cyclisation (see section 3.3) would allow formation of the tricyclic core *via* this route.

Deprotection was attempted using lithiated diphenylphosphine. Initial experiments made use of 20 equivalents of $LiPPh_2$, however after refluxing in THF for 15 hours, the material appeared to degrade. Reducing the number of equivalents and the reaction time, led to successful deprotection of two of the possible six methyl ethers, affording biaryl **160** in 44% yield. Deprotection is proposed to occur regioselectively at the most electron poor methyl ether (position 1, based on previous results), leading to bi-phenol **160**.[79] Unfortunately, gradually increasing the number of equivalents and variation of the reaction time led only to **160** or degradation. It is postulated that during the reaction, the build up of negative charge on the arene ring by the phenolate anion, prevented further reaction with the diphenylphosphine anion (Scheme 3.22).



Scheme 3.22: Deprotection conditions using diphenylphosphine.

Although this prevented isolation of the globally deprotected phenol, reports in the literature suggested that ceric ammonium nitrate (CAN), could facilitate oxidative removal of aromatic 1,4-methyl ethers to furnish the corresponding *p*-quinone.[90] With this in mind, phenol **160** was treated with five equivalents of CAN in MeCN and H_2O over three hours. Disappearance of starting material was observed by TLC analysis, however none of the desired quinone **155** was observed and the material had appeared to degrade under the reaction conditions (Scheme 3.23).

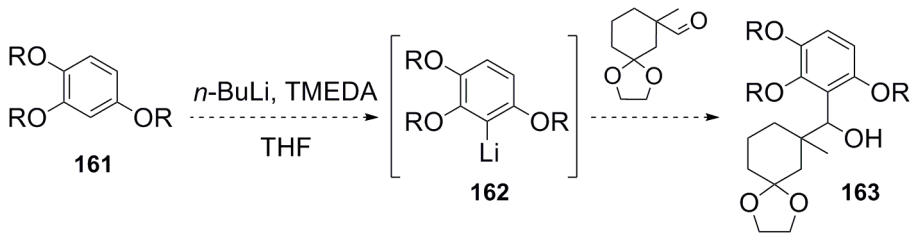


Scheme 3.23: Attempted oxidative cleavage of methyl ethers.

Although this method represents a suitable alternative strategy for the formation of the tricyclic core, it also presents some problems. Biaryl bond formation was successful *via* this route, however the resulting bis-ketone **157** was isolated in only moderate yield. It should also be considered that when carrying out this reaction on the 'real system' the increase in steric bulk, may reduce the yield of biaryl formation and in turn increase the quantity of by-product **158** being formed. Furthermore, as demonstrated by the results described above, deprotection of the methyl ethers has been found to be particularly difficult in late stage synthesis of these types of compounds.[91] It was therefore decided to continue studies towards the central core using the biomimetic route described previously (see sections 3.2, 3.3).

3.5 Protecting Group Studies

During studies towards the central core of **1**, it had become apparent that the use of methyl ether protecting groups was particularly problematic. Difficulties in removal of these groups had previously been encountered on systems within the Anderson group,[79] and in Katoh's synthesis of 8-*O*-methylpopolohuanone E (**131**).[66] It was therefore necessary to examine an alternative protecting group strategy. A variety of protecting groups for phenols and catechols were investigated with careful consideration of the conditions to which the substrate would be subjected. The current strategy involves installation of the phenolic unit by metallation of commercially available 1,2,4-trimethyoxybenzene (see section 3.1). It was proposed that lithiation of an alternative protected arene could allow installation of the phenolic portion of the molecule in a similar manner (Scheme 3.24).



Scheme 3.24: Proposed installation of the phenol unit.

Regioselectivity with respect to the lithiation step is aided by the presence of three highly coordinating methoxy groups on the aromatic ring, resulting in selective metallation at the 3-position of the arene. This type of directed metallation is also described as the complex induced proximity effect.[92] With this in mind, alternative protecting groups were chosen which could behave in a similar manner and allow regioselective lithiation to occur.

Initial studies focused on substituents that could be removed using a simple one-step procedure, which could vastly increase the efficiency of the final stages of the synthesis. A variety of suitable protected phenols were synthesised from 1,2,4-trihydroxybenzene using standard protection strategies (Figure 3.1).[90] In addition to the compounds shown here, generation of the corresponding tri-MOM protected phenol was also attempted, however only unreacted starting material and a mixture of the mono and bis protected products were recovered. Unfortunately, conducting the reaction with a large excess of (methoxy)methyl chloride at elevated temperatures, did not improve this result.

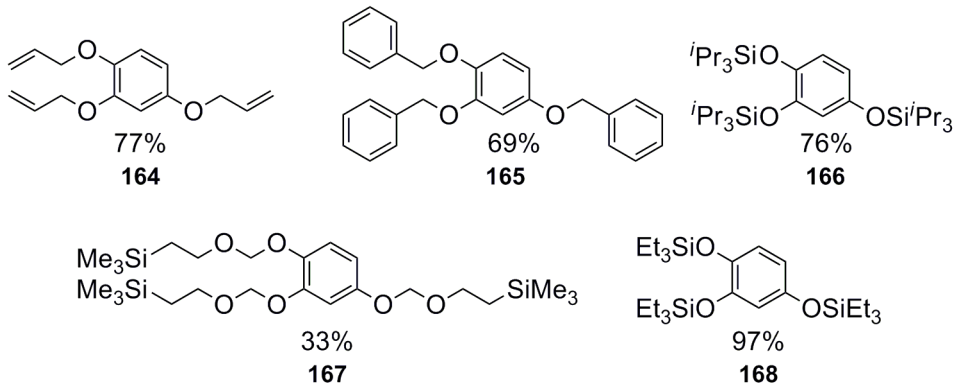
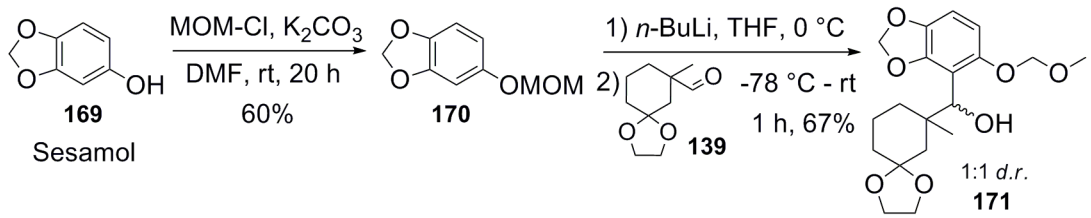


Figure 3.1: Synthesis of suitable protected phenols.

With protected phenols (**164-168**) in hand, each was subjected to the lithiation conditions employed previously. Each phenol was treated with *n*-butyllithium in THF at 0 °C followed by warming to room temperature and quenching with D_2O. Unfortunately attempts at lithiation using phenols **164-168** resulted in either complete

recovery of the starting material or degradation. Further studies were carried out using *t*-butyllithium as well as carrying out the reaction at –78 °C and quenching the reaction with MeI, benzaldehyde and aldehyde **139**, however all attempts proved unsuccessful.

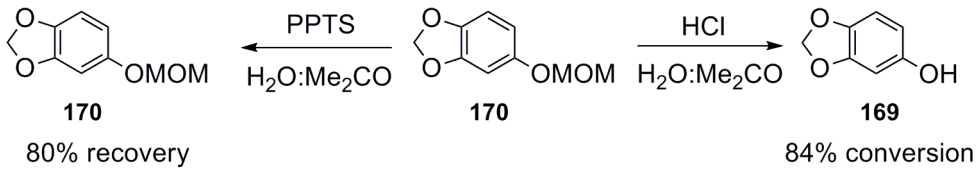
With disappointing results obtained for protected phenols **164**-**168**, a search for alternative strategies was conducted. It was found that successful lithiation of phenol **170** had previously been reported in the literature,[93] therefore it was postulated that **170** this could be utilised in this study. Phenol **170** was synthesised by MOM protection of the commercially available natural product sesamol **169** using standard conditions to afford **170** in 60% yield (Scheme 3.25). Treatment of **170** with *n*-butyllithium followed by reaction with aldehyde **139**, furnished alcohol **171** in an excellent 67% yield (Scheme 3.25).



Scheme 3.25: Synthesis and reactivity of MOM-sesamol **170**.

With production of alcohol **171** proving successful, synthesis of the model system incorporating these new protecting groups was required. However, due to problems encountered with removal of protecting groups from this system, it was essential that deprotection strategies were studied first. Using MOM-sesamol **170** as a model, removal of the MOM group was investigated. Treatment with HCl in H_2O:Me_2CO at room temperature overnight lead to 84% conversion to the desired phenol **169** (Scheme 3.26). Although this was successful, these conditions would also facilitate removal of the ketal protecting group used in this synthesis and would therefore result in unwanted MOM deprotection earlier in the synthesis. Despite this, reports in the literature had demonstrated the use of pyridinium *p*-toluene sulfonate (PPTS) to remove ketal groups on acid sensitive substrates.[94] With this in mind, treatment of MOM-sesamol **170** with PPTS in Me_2CO:H_2O (1:1), led to 80% recovery of the starting material with the remaining 20% residing as deprotected phenol **169**. This result was promising, however it was noted that ketal deprotection would require

careful analysis to ensure the reaction was terminated before removal of the MOM group began (Scheme 3.26).

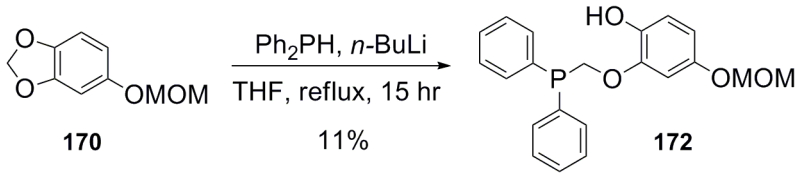


Scheme 3.26: MOM deprotection study.

The next challenge was to investigate removal of the acetal group, therefore MOM-sesamol **170** was subjected to a variety of deprotection conditions (Table 3.5). Reaction with BBr_3, $AlCl_3$/EtSH and PCl_5/H_2O all failed to produce any of the desired product and ^{1}H NMR analysis indicated only degradation products (Table 3.5, Entry 1-4). However, when utilising the previously used diphenylphosphine/*n*-butyllithium system, intermediate **172** was isolated in 11% yield (using 15 equivalents of $LiPPh_2$) (Table 3.5, Entry 5, Scheme 3.27). This result was promising, at it was envisaged that optimisation of the reaction conditions would enable complete deprotection. Unfortunately when increasing the number of equivalents to 20, the material appeared to degrade under the reaction conditions and none of the fully deprotected compound was observed. The regioselectivity was again assigned based on previous results.[79]

Entry	Reagents	Conditions	Result
1	$AlCl_3$, EtSH	0 °C - rt	degradation
2	BBr_3	CH_2Cl_2, -78 °C - rt	degradation
3	BBr_3	CH_2Cl_2, -78 °C	degradation
4	PCl_5, H_2O	toluene, reflux, 15 h	degradation
5	Ph_2PH, *n*-BuLi	THF, reflux, 15 h	**172**

Table 3.5: New deprotection conditions.

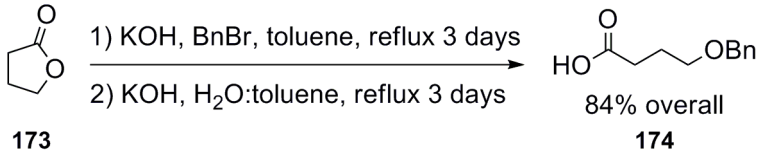


Scheme 3.27: Incomplete deprotection.

It was postulated that when utilising these conditions on the model system or 6'-hydroxyarenarol (**7**), full deprotection of the acetal group might be possible. However, the yield of this reaction on the model system was particularly poor and it was therefore suggested that in fact the most appropriate strategy would involve the original methyl ether protection and that deprotection would be conducted *via* the three-step approach (see section 3.1). With these results in hand, focus turned towards the synthesis of 6'-hydroxyarenarol (**7**).

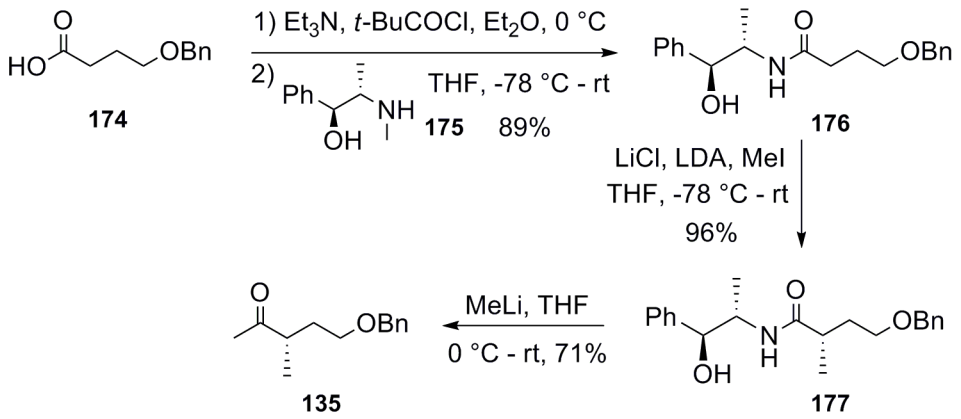
3.6 Synthesis of Chiral Iodide

The first challenge with respect to the synthesis of 6'-hydroxyarenarol (**7**) was to achieve an efficient synthesis of iodide **83** in an enantioselective manner. Initial studies were based on previous work within the Anderson group,[79] which focused on the synthesis of methyl ketone **135** *via* asymmetric alkylation. Ring opening and benzyl protection of γ-butyrolactone **173** was carried out using KOH and benzyl bromide at reflux for three days, to afford the desired carboxylic acid **174** in excellent 84% yield (Scheme 3.28).



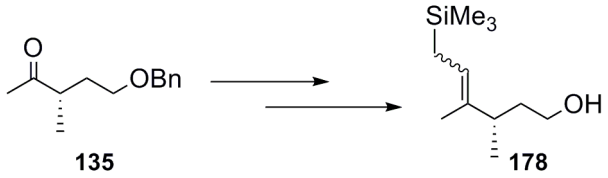
Scheme 3.28: Ring opening of γ-butyrolactone.

With acid **174** in hand, a suitable auxillary for use in the asymmetric alkylation reaction was chosen. Myers' *pseudo*-ephedrine auxillary **175** had proved successful on this system in previous work,[55] therefore the synthesis was continued using this methodology. Installation was carried out *via* treatment of acid **174** with triethylamine and pivaloyl chloride to afford the mixed anhydride intermediate. This was followed by addition of the auxillary **174** to afford *pseudo*-ephedrine amide **176** in 89% yield. Alkylation was then carried out using lithium chloride, LDA and methyl iodide to furnish the desired product **177** in an excellent 96% yield. Removal of the *pseudo*-ephedrine auxillary was then achieved using methyllithium in THF to afford the enantiopure intermediate methyl ketone **135** in 71% yield (Scheme 3.29).[95]



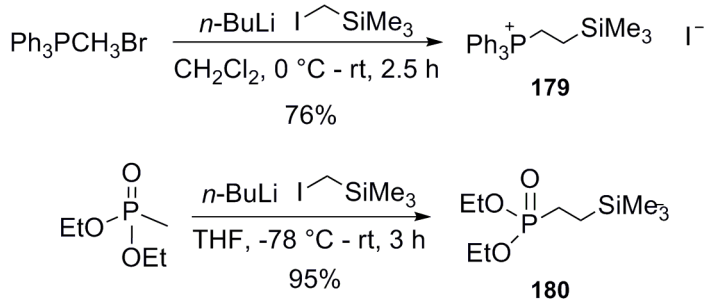
Scheme 3.29: Asymmetric alkylation and removal of *pseudo*-ephedrine auxillary.

The next stage required conversion of **135** to the desired allylsilane **178** (Scheme 3.30). Previous work had investigated this process, attempting olefination using a standard phosphonium reagent.[79] Unfortunately, these conditions led only to the recovery of unreacted starting material in all cases and a search of the literature demonstrated that particularly low yields have been reported for this reaction on hindered ketones similar to **135**. [96]



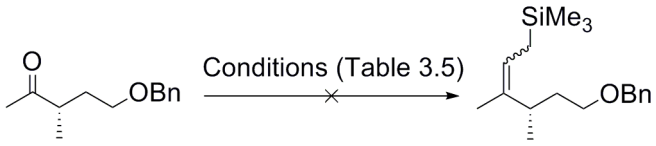
Scheme 3.30: Desired transformation to allylsilane.

In an extension of these studies, it was postulated that isolation of the phosphonium salt **179** (previously formed *in situ*) prior to olefination, might enable the reaction to proceed. In addition, it was also proposed that the use of the corresponding phosphonate **180** could allow reaction to occur on this system. Synthesis of phosphonium **179** was carried out *via* treatment of methyltriphenylphosphonium bromide with *n*-butyllithium, followed by addition of iodo(methyl)trimethylsilane to afford the desired phosphonium salt **179** in 76% yield as a crystalline white solid. In turn, phosphonate **180** was synthesised from diethoxymethyl phosphonate in the same manner to afford silane **180** in 95% yield (Scheme 3.31). Fortunately, it has been reported in the literature,[74] that the geometry of the resulting alkene in this olefination reaction, did not play a part in the high diastereoselectivity observed in the Hosomi-Sakurai reaction, conducted later in the synthesis. Therefore olefination was not required to proceed with selectivity with respect to the alkene geometry.



Scheme 3.31: Synthesis of phosphonate **179** and phosphonium **180**.

The proposed Wittig reaction was performed using a variety of conditions (Table 3.6). Reactions were attempted using *n*-butyllithium, in diethyl ether at 0 °C, as well as THF at reflux, both of which afforded recovery of unreacted starting material (Table 3.6, Entry 1-2). When changing the base from *n*-butyllithium to methyllithium, complete recovery of ketone **135** was also observed (Table 3.6, Entry 3). The use of *t*-BuOK in toluene at reflux had previously been successfully utilised for the formation of particularly hindered *exo*-cyclic alkenes,[97] however, when attempting these conditions the same result was achieved (Table 3.6, Entry 4). Finally, phosphonate **180** was used, however no difference in reactivity was observed when compared to the corresponding phosphonium (Table 3.6, Entry 5).



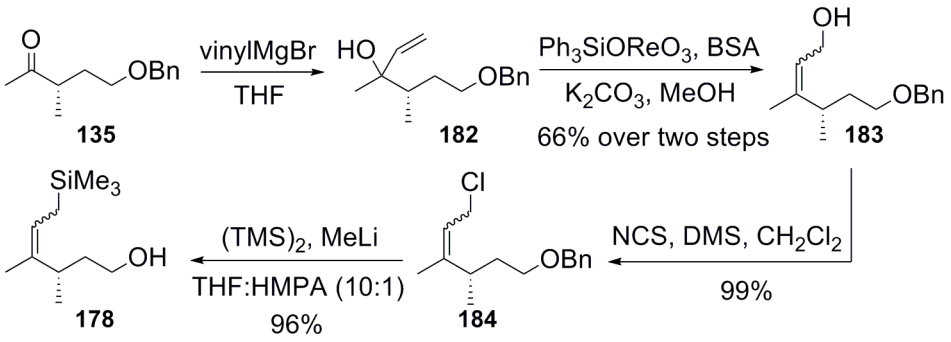
135 **181**

Entry	Reagent	Base	Conditions
1	**179**	*n*-BuLi	Et_2O, 0 °C - rt
2	**179**	*n*-BuLi	THF, 0 °C - reflux
3	**179**	MeLi	THF, 0 °C - reflux
4	**179**	*t*-BuOK	toluene, reflux
5	**180**	*n*-BuLi	THF, -78 °C - reflux

Table 3.6: Olefination conditions for allylsilane formation.

With olefination proving ineffective, alternative routes were investigated. Previous work had examined a number of methods, which resulted in poor yields of the allylsilane and eventually, a four-step route to the unprotected alcohol **178** was

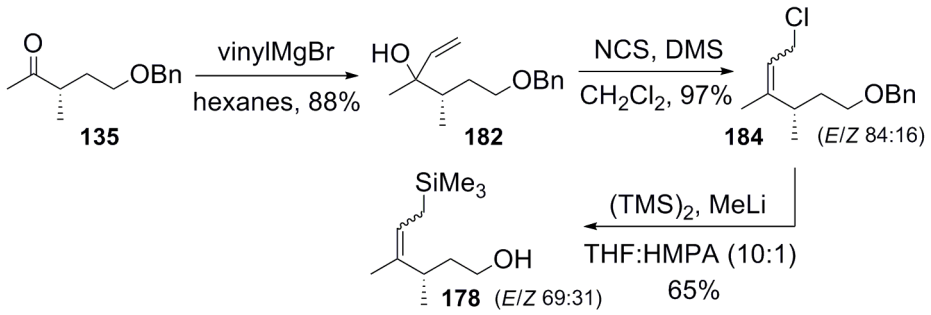
developed.[79] This route required Grignard addition of vinylmagnesium bromide to methyl ketone **135**, affording allylic alcohol **182**. Without purification, this material was subjected to allylic rearrangement with $Ph_3SiOReO_3$ and BSA to afford alcohol **183**.[98] Subsequent treatment with NCS and dimethyl sulfide furnished the corresponding chloride, followed by addition of TMSLi (formed *in situ* from hexamethyldisilane and methyllithium) successfully gave rise to the desired allylsilane **178** with fortuitous removal of the benzyl protecting group (Scheme 3.32).



Scheme 3.32: Previous route to allylsilane.

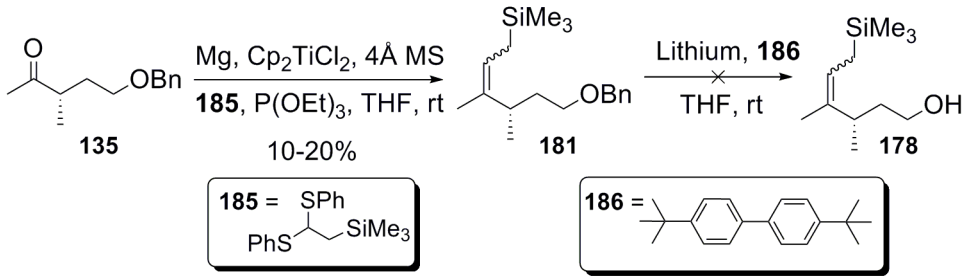
Although this provided a solution to the installation of the allylsilane functionality, the route was particularly lengthy. Further examination of the desired transformation was therefore required. Initial studies focussed on the previously developed route (Scheme 3.32), which enabled material to be progressed to subsequent stages of the synthesis. Grignard addition to ketone **135** proceeded smoothly and purification was carried out by filtering through a plug of silica to furnish **182** in 88% yield. Synthesis of $Ph_3SiOReO_3$ was then achieved using literature procedures,[99] which required use immediately after preparation due to apparent degradation in air. Rearrangement proceeded smoothly followed by desilylation of the resulting TMS protected primary alcohol with K_2CO_3 to afford allylic alcohol **183** in 66% yield (*E*/*Z* 80:20). At this stage it was postulated that the rearrangement reaction could be eliminated from the synthetic route if allylic alcohol **182** could be directly converted into chloride **184** by treatment with NCS and dimethyl sulfide. This was attempted successfully, leading to isolation of the corresponding chloride **184** in 97% yield without need for purification (*E*/*Z* 84:16). This transformation delightfully removed a chemical step from the synthesis as well as omitting the need for synthesis of the unstable rhenium catalyst. With chloride **184** in hand, treatment of the material (as a mixture of geometric isomers) with TMSLi as described previously, furnished the desired alcohol **178** in 65% yield (*E*/*Z* 69:31) (Scheme 3.33). Although this study had led to

significant improvements when compared to the previous synthesis, some alternative strategies were also examined.



Scheme 3.33: Improved route to allylsilane **178**.

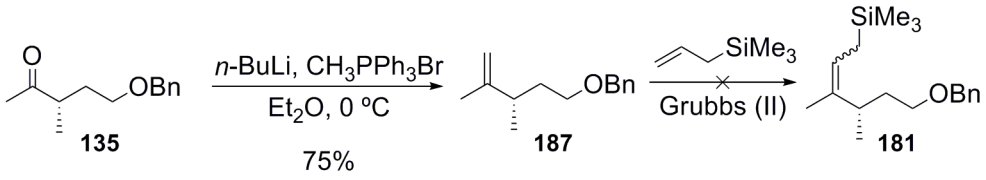
A search of the literature had revealed that Takeda and co-workers,[100] had successfully installed allylsilane derivatives using the complex formed from Cp_2TiCl_2 and $P(OEt)_3$ in the presence of magnesium and sulfide **185**. The required sulfide **185** was prepared using literature procedures,[101] and the reported procedure attempted using methyl ketone **135**. Upon isolation and purification, this process was found to furnish only 10-20% yields of the corresponding allylsilane **181** as an unquantifiable mixture of double bond isomers. It was postulated that the low isolated yield was due to difficulties in removing the inorganic salts during work-up and purification on silica. Despite the low yielding reaction, subsequent debenzylation was attempted using LiDBBP (lithium di-*tert*-butyl-biphenyl).[102] Formation of a bright green solution during the reaction indicated formation of the desired radical anion, however none of the desired product was isolated (Scheme 3.34). Due to the low yield in the olefination reaction and difficulties in debenzylation, this route was not pursued.



Scheme 3.34: Attempted allylsilane installation and debenzylation.

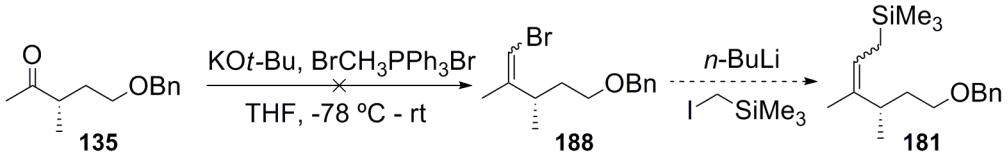
With this method providing insufficient yields for the silane introduction, it was postulated that a simple methylenation reaction using triphenylphosphonium bromide could be carried out. The resulting olefin **187** could then be further manipulated to afford the desired structure *via* cross metathesis (Scheme 3.35). Treatment of methyl

ketone **135** with the ylide formed from treatment of CH_3PPh_3Br with *n*-butyllithium (10 equivalents), allowed successful formation of the desired alkene **187** in 75% yield. With this in hand the proposed metathesis reaction was attempted. Reactions were carried out using both Grubb's (II) and Grubb's/Hoveyda catalysts with allylsilane, however both reactions were found to result in homocoupling of allylsilane. Slow addition of the allylsilane *via* syringe pump and conducting the reaction in THF at elevated temperatures, also provided no evidence that the metathesis reaction was occurring (Scheme 3.35).



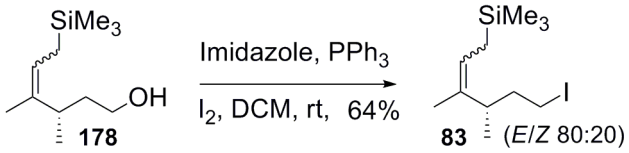
Scheme 3.35: Attempted metathesis route to allylsilane **181**

Although the proposed metathesis route proved unsuccessful, the success of methylenation to form **187** was intriguing. It was suggested that if olefination to form bromide **188** could also be performed, then a subsequent lithium halogen exchange followed by reaction with iodo(methyl)trimethylsilane could enable synthesis of allylsilane **181**. Treatment of methyl ketone **135** with $BrCH_2PPh_3Br$ and *t*-BuOK unfortunately led to the recovery of starting material (Scheme 3.36).



Scheme 3.36: Alternative route to allylsilane **181**.

Due to the results described above, continuation of the synthesis was necessary using the three-step route (Scheme 3.33). With alcohol **178** in hand, conversion to the corresponding iodide was conducted by treatment with I_2, imidazole and triphenylphosphine in MeCN which successfully afforded iodide **83** in 76% yield (*E*/*Z* 80:20) (Scheme 3.37). With this in hand, focus was turned towards the synthesis of the *cis*-decalin motif found in popolohuanone E (**1**).

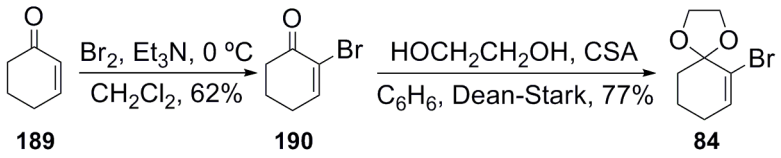


Scheme 3.37: Formation of the desired intermediate iodide **83**.

3.7 Synthesis of 6'-Hydroxyarenarol

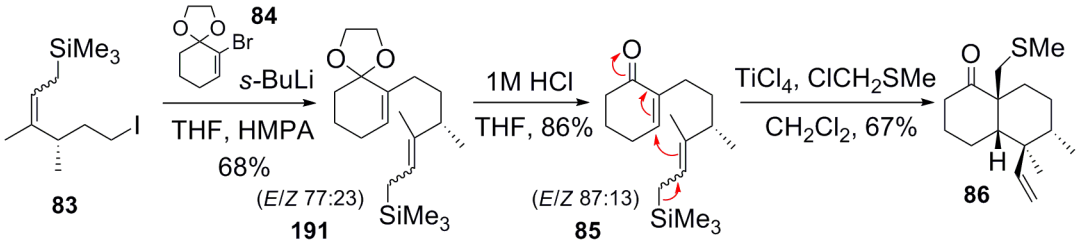
With the synthesis of iodide **83** fully explored, attention turned to formation of the *cis*-decalin ring system and subsequently the installation of the phenolic portion found in 6'-hydroxyarenarol (**7**).

Synthesis of bromide **84** was achieved using literature procedures.[103] Bromination of cyclohexenone **189** followed by *in situ* elimination of HBr furnished α-bromo ketone **190** in 62% yield. It was noted that bromide **190** appeared to undergo polymerisation if left for long periods of time (>1 hour) at room temperature and was therefore stored at –20 °C. Subsequent ketal protection under Dean-Stark conditions using ethylene glycol and CSA in benzene afforded bromide **84** in 77% yield (Scheme 3.38).



Scheme 3.38: Synthesis of bromide **84**.

The proposed coupling reaction was then examined. Treatment of bromide **84** with 2.4 equivalents of *s*-butyllithium in THF followed by addition of the iodide **83** afforded coupled product **191** in 68% yield (*E*/*Z* 77:23). This reaction was found to be particularly capricious and it was found that slow addition of the *s*-butyllithium was necessary to achieve successful lithium halogen exchange and hence formation of coupled product **191**. Smooth removal of the ketal protecting group with 1M HCl in THF afforded the Hosomi-Sakurai precursor **85** in excellent 86% yield (*E*/*Z* 87:13). The next challenge was to carry out Hosomi-Sakurai reaction to form the *cis*-decalin bicyclic. Treatment of a solution of $TiCl_4$ with a solution of sulfide and unsaturated ketone **85** allowed successful reaction with intermolecular trapping of the resulting enolate with chloro(methyl)methylsulfide to afford *cis*-decalin **86** in 67% (Scheme 3.39).



Scheme 3.39: Construction of the key *cis*-decalin structure **86**.

This highly diastereoselective reaction had previously been developed on these systems by Tokoroyama and co-workers,[74] who suggested a two fold explanation for the observed selectivity. The authors initially considered the cyclisation of allylsilane **85**. If it is assumed that the emerging six membered ring assumes a chair like configuration in the transition state, two possible orientations are possible due to the position of the allylsilane group with respect to the cyclohexenone ring (*exo* **192** and *endo* **193**). Of these, the authors postulated that *exo* attack **192** will be favoured when considering steric and electronic factors and the knowledge that the linear confirmation present in **192** is favoured in a variety of comparable reactions.[104] The authors also noted, that the geometry of the allylsilane double bond would not effect the outcome of selectivity. Assuming the *exo* position of the allylsilane is favoured, two confirmations would be possible with respect to the C-7 methyl group. When considering the 1,3-allylic strain present in **194**, it was suggested that configuration **192** would be the most favourable, which explains the observed stereoselectivity in the newly formed ring (Figure 3.2).

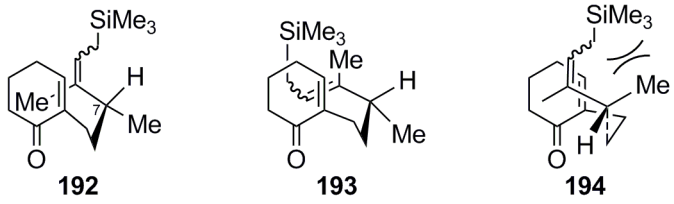
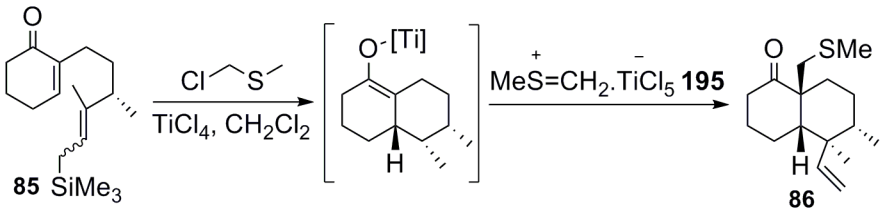


Figure 3.2: Possible transition states for the Hosomi-Sakurai reaction.

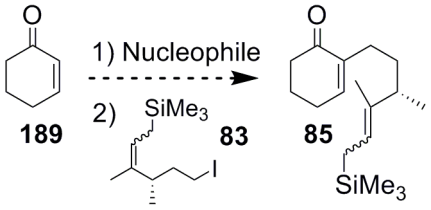
The authors later used this methodology towards the synthesis of the *cis*-clerodane structure found in the natural product Linaridial.[105] They reported that trapping of the enolate resulting from the Hosomi-Sakurai reaction was particularly difficult on this system due to steric interactions. After extensive experimentation it was found that two equivalents of $TiCl_4$ in the presence of chloro(methyl)methylsulfide successfully afforded the desired product **86** in 77%. This increased reactivity was ascribed to the formation of species **195**, which the authors suggested would be highly reactive and

also less sterically demanding. For these reasons, investigation into alternative electrophilic reagents for this process was not carried out at this time. The authors also suggested that the selectivity with respect to the formation of the *cis* decalin (as opposed to the *trans*-decalin), originates from electrophilic attack from the convex side of the molecule (Scheme 3.40).



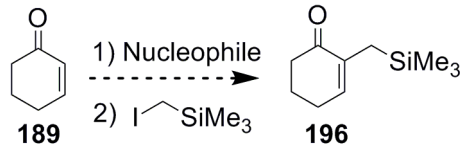
Scheme 3.40: Intramolecular trapping with chloro(methyl)methylsulfide.

To continue studies towards a more efficient route to 6'-hydroxyarenarol (**7**), alternative routes to the Hosomi-Sakurai precursor **85** were considered. It was suggested that use of a Baylis-Hillman type reaction could be utilised for this transformation. It is known in the literature than addition of an amine base to α-β-unsaturated ketones can be conducted followed by intermolecular trapping of the resulting enolate with a suitable alkyl halide.[106] It was proposed that this reaction could be applied to coupling between cyclohexenone **189** and iodide **83** to provide the Hosomi-Sakurai precursor **85** (Scheme 3.41). If this was successful, the two step synthesis of bromide **84**, as well as deprotection of the ketal after the coupling reaction (as in the current synthesis) would be omitted, increasing the efficiency of this stage of the synthesis.



Scheme 3.41: Proposed Baylis-Hillman reaction.

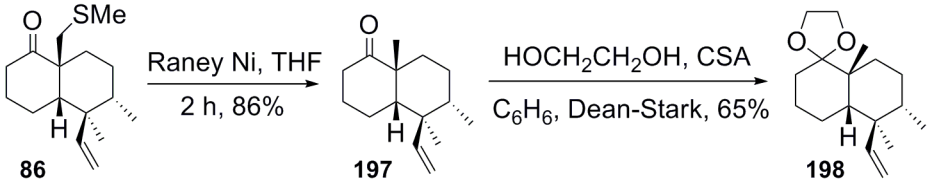
With this in mind, Baylis-Hillman type conditions were attempted using iodo(methyl)trimethylsilane as a simple model system for iodide **83**. Initial studies involved reaction of cyclohexenone with a number of amine and phosphine nucleophiles, followed by quenching with iodo(methyl)trimethylsilane. A variety of solvents and additives were utilised in the reaction, however all attempts resulted in recovery of starting material (Table 3.7).



Entry	Base	Additives	Solvent
1	DABCO	None	CH_2Cl_2
2	PBu_3	KOH, $BnEt_3NCl$	*iso*-butyroalcohol
3	imidazole	--	CH_2Cl_2, H_2O
4	$NaHCO_3$	L-proline	DMF/H_2O
5	imidazole	L-proline	DMF

Table 3.7: Baylis-Hillman conditions.

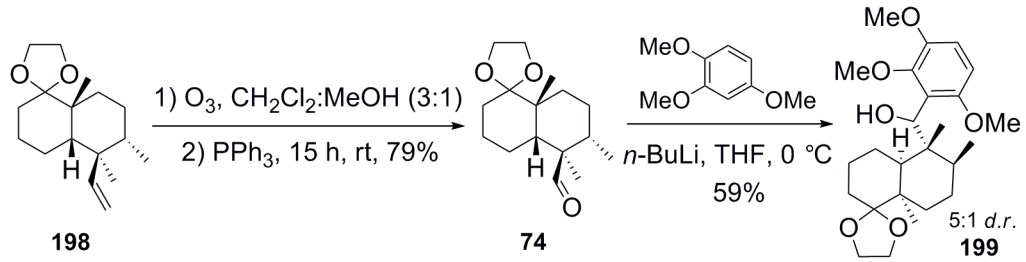
Despite attempts to reduce the number of steps involved in the synthesis of the decalin core, the previously used Hosomi-Sakurai reaction had proved highly efficient and therefore focus turned towards installation of the phenolic portion of the molecule. Desulfurisation of *cis*-decalin **86** to afford the methyl stereocentre present in popolohuanone E (**1**), was attempted. It had previously been reported,[107] that deactivation of Raney nickel by refluxing in Me_2CO could allow removal of the sulfide, whilst keeping the terminal alkene intact. Deactivation using this method was carried out, followed by solvent exchange to THF and addition of decalin **86**. This allowed successful desulfurisation, to furnish the desired decalin **197** in 86% yield. Re-protection of the ketone was then performed using ethylene glycol and CSA in refluxing benzene under Dean-Stark conditions to afford ketal **198** in 65%. A large quantity of unreacted ketone **197** was also isolated, therefore the reaction was attempted using increased equivalents of ethylene glycol and CSA, as well as using toluene as the solvent. Unfortunately, no improvement in yield was observed (Scheme 3.42).



Scheme 3.42: Desulfurisation and ketone protection.

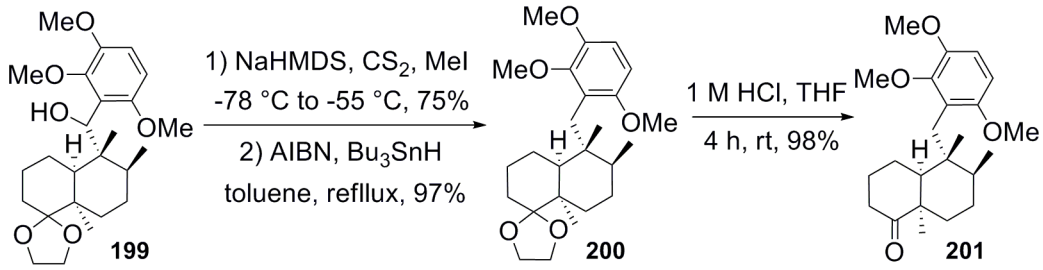
Ozonolysis of the terminal alkene was then required. Treatment of alkene **198** with ozone followed by addition of triphenylphosphine, afforded the desired aldehyde **74**

in 79% yield. Subsequent reaction of aldehyde **74** with lithiated 1,2,4-trimethoxybenzene as developed previously, allowed formation of alcohol **199** in 59% yield as a 5:1 mixture of diastereoisomers. It is interesting to note that when this reaction was carried out on the model system, warming to room temperature was required for successful reaction, however when using the *cis*-decalin system, the product appeared to degrade on warming. For this reason, the reaction was quenched with H_2O at 0 °C (Scheme 3.43).



Scheme 3.43: Installation of the phenolic portion.

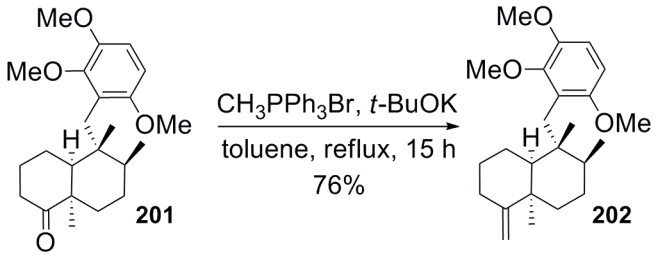
Benzylic deoxygenation was then attempted using conditions previously utilised within the Anderson group and by Katoh *et al*.[66] Conversion to the corresponding methyl xanthate using NaHMDS, CS_2 and MeI was effective in 75% yield. Subsequent deoxygenation using AIBN and tributyltin hydride afforded the deoxygenated product **200** in excellent 97% yield. Deprotection of the ketal was then performed by treatment with 1M HCl in THF to afford ketone **201** in 98% yield (Scheme 3.44).



Scheme 3.44: Deoxygenation and deprotection conditions.

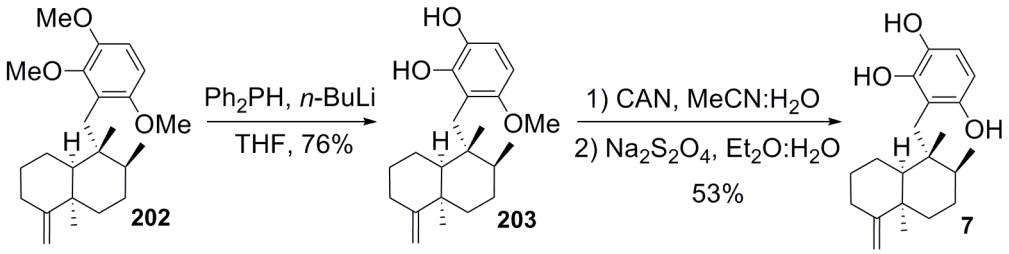
With ketone **201** in hand, final steps towards the synthesis of 6'-hydroxyarenarol (**7**) required installation of the *exo*-cyclic alkene and deprotection of three methyl ethers to furnish the oxidative dimerisation precursor. Initial experiments focused on methylenation using triphenylphosphonium bromide and *t*-BuOK. This reaction was found to be unsuccessful, with unreacted starting material being recovered and it was postulated that the ylide was not forming under the reaction conditions. Eventually it

was found that this was due to impure *t*-BuOK and when performing the reaction using freshly purchased *t*-BuOK, methylenation was achieved to afford alkene **202** in 76% yield (Scheme 3.45).



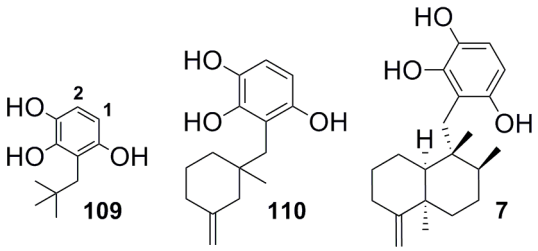
Scheme 3.45: Installation of *exo*-cyclic alkene.

With the *exo*-cyclic alkene successfully installed, deprotection was attempted using lithiated diphenylphosphine as conducted previously on the model system. This reaction afforded the desired mono-methylated phenol **203** in 76% yield. Subsequent oxidation to the corresponding *p*-quinone **112** was performed using CAN in MeCN:H_2O (2:1) followed by direct reduction to the desired 6'-hydroxyarenarol (**7**) using $Na_2S_2O_4$. This afforded the coupling precursor 6'-hydroxarenarol (**7**) with a crude yield of 53% over two steps (Scheme 3.46).



Scheme 3.46: Final deprotection to afford 6'-hydroxyarenarol (**7**).

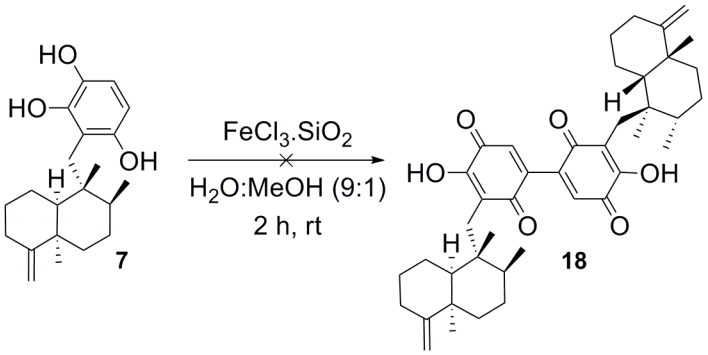
Studies on model system **132** had shown that phenols of this type were particularly susceptible to spontaneous oxidation, affording the corresponding *p*-quinone. Fast purification was therefore attempted (<15 minutes on the column), however re-oxidation to the corresponding *p*-quinone **112** was observed. For this reason, 6'-hydroxyarenarol (**7**) was used without purification. Comparison of ^{1}H NMR data obtained for **7** with previously synthesised phenol **110** (used in the model system study) and **109** (used in previous studies) showed excellent correlation (Table 3.8).



Entry	Compound	ArH (1) ppm	ArH (2) ppm
1	**109**[76]	6.27	6.63
2	**110**	6.27	6.63
3	**7**	6.20	6.60

Table 3.8: Comparison of ^{1}H NMR data.

With the desired coupling precursor successfully synthesised, oxidative dimerisation was attempted. Phenol (**7**) was subjected to the conditions developed on the model system using $FeCl_3.SiO_2$ in H_2O:MeOH (9:1). Analysis of the crude reaction mixture by ^{1}H NMR showed complete consumption of starting material and a singlet in the aromatic region indicating promising evidence for dimerisation. Interestingly there was no evidence of mono-quinone **112**, which was the only product observed during previous studies.[79] After flash column chromatography, ^{1}H NMR analysis of the major compound showed promising peaks for a dimerised product, however unfortunately mass spectrometry showed no sign of the desired bis-quinone **18** or compounds of a similar mass (Scheme 3.47).



Scheme 3.47: Attempted oxidative dimerisation.

In addition to this study, when attempting to reduce intermediate quinone **112** to the desired 6'-hydroxarenarol (**7**), formation of the expected phenol **7** was not observed

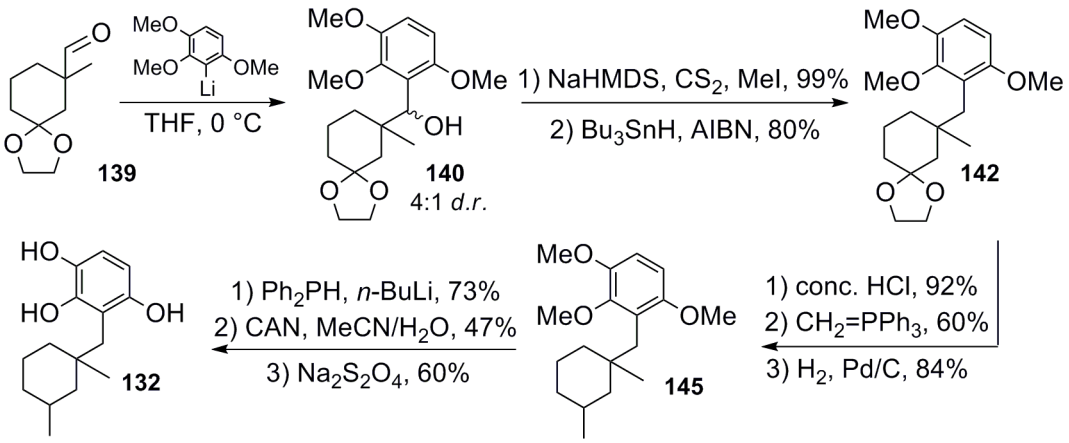
and formation of an unknown by-product was seen. This material also demonstrated promising signs of dimerisation with a singlet in the aromatic region and presence of the *exo*-cyclic alkene and benzylic CH_2 by ^1H NMR. In addition, analysis by mass spectrometry showed peaks corresponding to a dimerised compound with a mass of 656, two more than the desired bis-quinone **18** (654). As this represented promising evidence of a dimerisation taking place, the material was subjected to cyclisation conditions using K_2CO_3 in deuterated Me_2CO, however unfortunately, no reaction was observed.

These final experiments have unfortunately shown that bis-quinone **18**, required for completion of the total synthesis, was not observed during these studies. However, the results have provided some evidence to suggest that a dimerisation reaction was occurring under the developed oxidative conditions. The small quantity of material available at this stage made characterisation of the isolated material particularly difficult, therefore synthesis of larger quantities of phenol (**7**) would be necessary for a thorough investigation of this process and completion of the total synthesis.

4.0 Conclusions and Future Studies

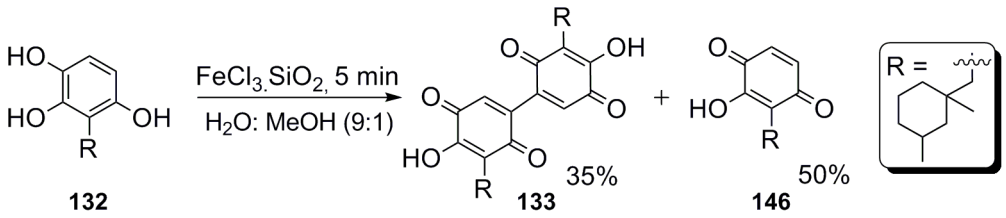
4.1 Conclusions

This chapter has described work towards the total synthesis of popolohuanone E (**1**). Studies began with the successful 12 step synthesis of a model system **132** in an overall yield of 3.1%. The synthesis involved construction of aldehyde **139** followed by reaction with lithiated 1,2,4-trimethoxybenzene to afford alcohol **140**. Deoxygenation and removal of the ketal protecting group were followed by methylenation, achieved in good yield. Subsequent removal of the resulting alkene was then conducted to avoid intramolecular cycloaddition as seen previously.[79] With this in hand, deprotection of the methyl ethers *via* the previously developed route, afforded the model target **132** (Scheme 4.0).



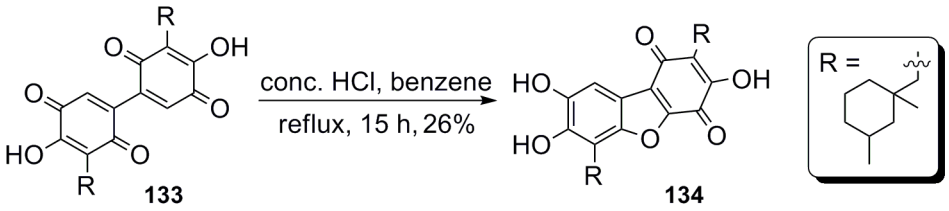
Scheme 4.0: Model system synthesis.

Phenol **132** was then used to investigate the proposed oxidative dimerisation reaction. A variety of reagents and conditions were examined, however the best results were obtained when focussing on the use of $FeCl_3.SiO_2$ as the oxidant. Reaction conditions using this reagent were optimised to give the desired bis-quinone **133** in 35% yield with the majority of the remaining material residing as the mono-quinone **147** (50%) (Scheme 4.1).



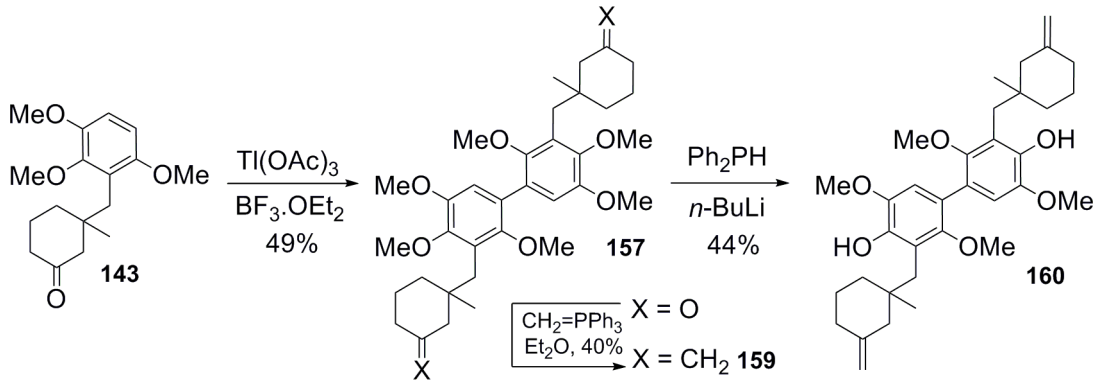
Scheme 4.1: Oxidative dimerisation conditions.

With the biaryl bond successfully installed, cyclisation to complete the tricyclic core of popolohuanone E (**1**) was investigated. It was found that a base catalysed cyclisation, resulted in isolation of a complex mixture of products. However, use of concentrated HCl in refluxing benzene, allowed formation of the dibenzofuran core **134** in 26% yield as a dark purple solid, completing the biomimetic synthesis on this system (Scheme 4.2).



Scheme 4.2: Formation of the tricyclic core.

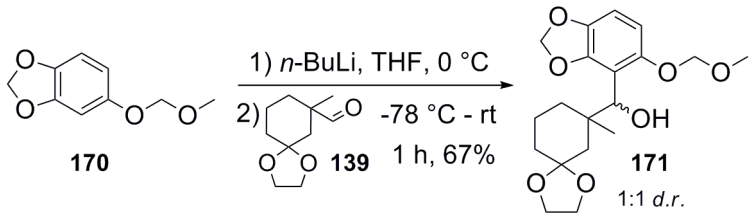
Alternative strategies towards the central core were also examined. Biaryl coupling using $Tl(OAc)_3$ furnished bis-ketone **157** in 49% yield, which was followed by double methylenation to afford the corresponding bis-alkene **159** in 40% yield. With this in hand, deprotection was attempted, however unfortunately only two of the six methyl groups were removed successfully (Scheme 4.3).



Scheme 4.3: Biaryl coupling strategy towards the central core.

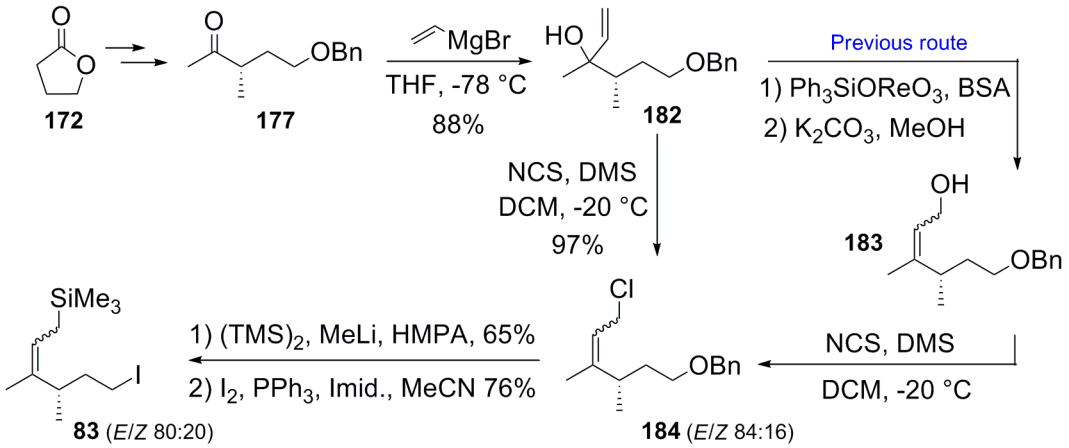
Alternative phenol and catechol protecting groups were also examined. Installation of appropriate protected phenols was attempted by reaction with aldehyde 1**39**,

however success was only achieved when using MOM-sesamol **170** (Scheme 4.4). Lithiation of **170** followed by reaction with aldehyde **139** successfully afforded the corresponding *neo*-pentyl alcohol **171** in 67% yield. Although this result was encouraging, it was subsequently found that when removal of the catechol group was attempted, only partial deprotection, or degradation was observed in all cases.



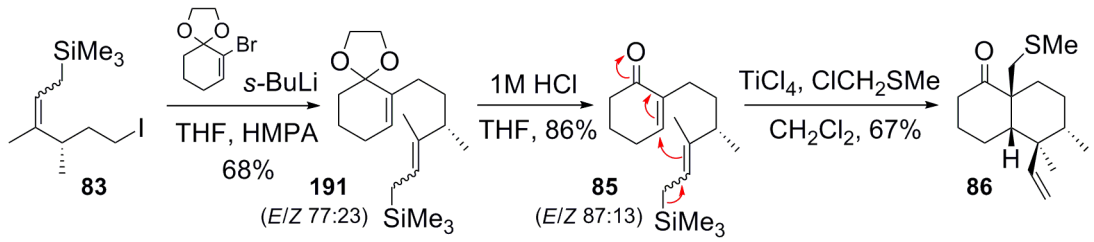
Scheme 4.4: Alternative protecting group strategy.

Focus then turned towards the synthesis of iodide **83**. A variety of studies were conducted to improve the existing route, which culminated in removal of a challenging rearrangement step, allowing direct conversion of tertiary alcohol **182** to the corresponding allylic chloride **184** (Scheme 4.5).



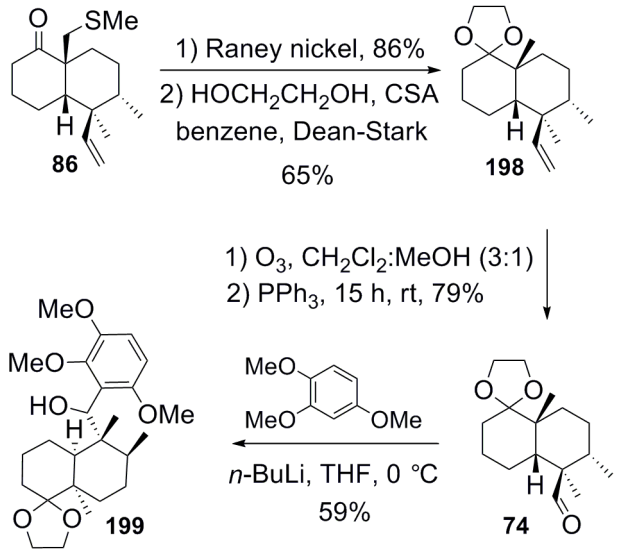
Scheme 4.5: Improvements to iodide synthesis.

With iodide **83** available, lithiation of bromide **84** followed by reaction with iodide **83**, afforded coupled intermediate **191**. Ketal deprotection revealed the corresponding ketone **85** and hence the desired Hosomi-Sakurai precursor. Hosomi-Sakurai reaction proceeded smoothly with intermolecular trapping of the resulting enolate to yield the *cis*-decalin structure **86** as a single diastereoisomer (Scheme 4.6).



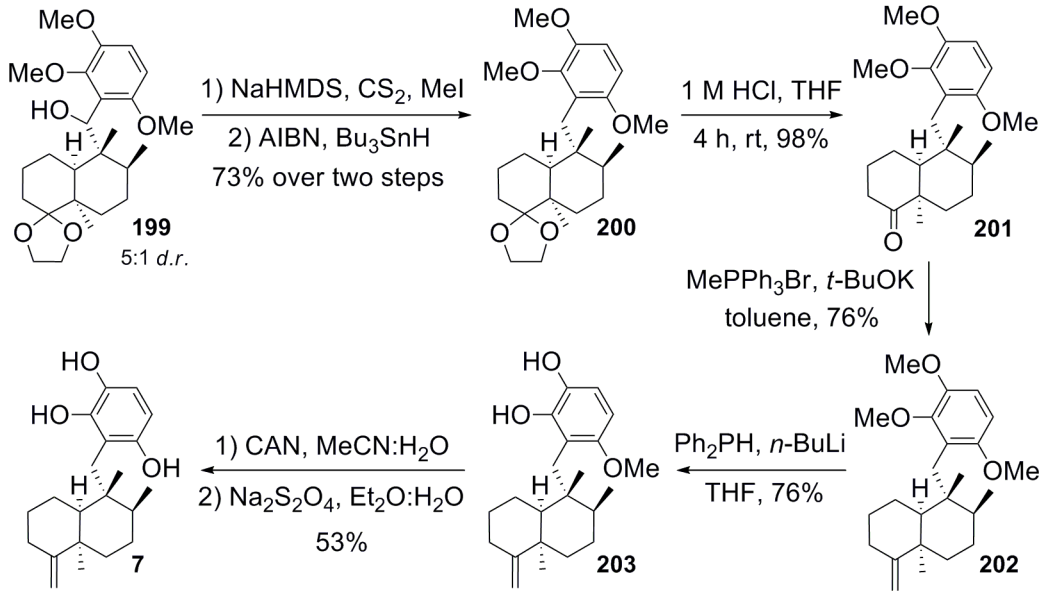
Scheme 4.6: Construction of the *cis*-decalin core.

Steps were then conducted to synthesis intermediate aldehyde **74** in an efficient manner. Desulfurisation and subsequent re-protection of the ketone afforded ketal **198** in good yield. Ozonolysis was then performed to furnish aldehyde **74**, which was subjected to lithiated 1,2,4-trimethoxybenzene, affording alcohol **199** in 59% yield (Scheme 4.7)



Scheme 4.7: Installation of phenolic portion.

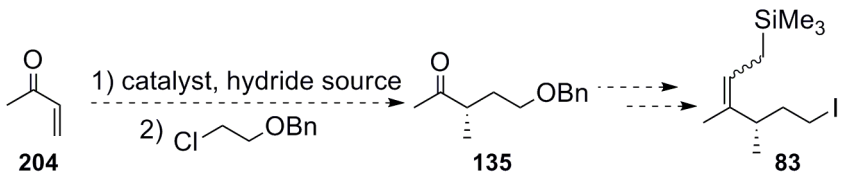
The final steps towards the synthesis of 6'-hydroxyarenarol (**7**) were then examined. Deoxygenation, was achieved as in the model system to afford **200** in 73% over two steps. Ketal deprotection and methylenation then afforded, the trimethoxy-analogue of the proposed precursor (**202**). Finally deprotection was carried out using the three-step procedure developed previously to afford 6'-hydroxyarenarol (**7**) (Scheme 4.8). Phenol (**7**) was subjected to the oxidative dimerisation conditions developed on the model system, however none of the desired bis-quinone **18** was observed.



Scheme 4.8: Final steps towards 6'-hydroxyarenarol (**7**).

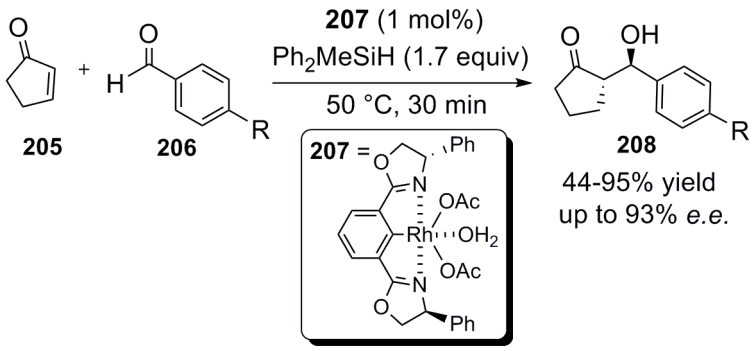
4.2 Future Studies

When considering potential for future studies within this research area, there are a number of elements that could be improved. The current route to iodide **83** involves two transformations, which require lengthy procedures. Firstly, installation of the single stereocentre present in iodide **83** is currently performed using a chiral auxillary-based approach. It is suggested that installation of this stereocentre could be achieved in a more efficient manner using a chiral catalyst or ligand. Hydride reduction of an enone, followed by asymmetric alkylation of the resulting enolate could facilitate this transformation. Hydride addition to commercially available methyl vinyl ketone, followed by intermolecular trapping of the resulting enolate with 1-chloro-2-benzyloxyethane (or a derivative there of) could provide enantiomerically pure ketone **135** used in the current synthesis (Scheme 4.9).



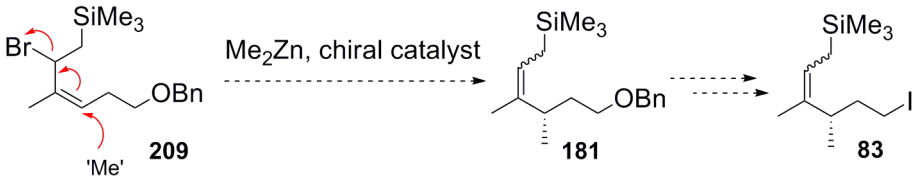
Scheme 4.9: Alternative strategy to methyl ketone intermediate **135**.

The asymmetric hydride reduction of enones is well documented in the literature,[108] with some examples demonstrating alkylation *via* intermolecular trapping of the resulting enolate (Scheme 4.10).[109] It is proposed that this method could enable formation of iodide **83** in five steps.



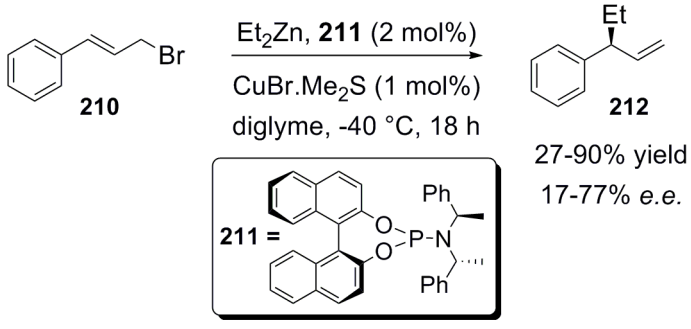
Scheme 4.10: Literature precedence for the reduction/alkylation reaction.

The second transformation that has presented problems in the current synthesis, involves construction of the allylsilane portion. It is thought that this could be more successfully carried out by SN_2' reaction of a suitable 'methyl' nucleophile to allylic halides such as **208** (Scheme 4.11). This procedure could install the essential allylsilane and create the crucial methyl stereocentre, to afford enantiopure silane **181**.



Scheme 4.11: Alternative strategy for installation of the allylsilane.

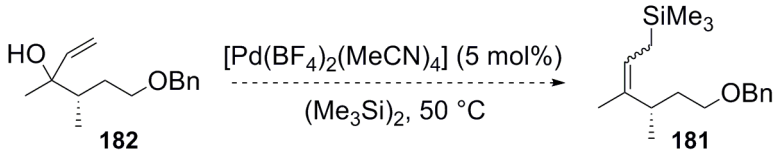
Reports in the literature have demonstrated suitable SN_2' reactions of this type using phosphoramidite ligands with dialkylzinc reagents (Scheme 4.12).[110] If successful on the current system, this strategy could lead to an efficient improved synthesis of iodide **83**.



Scheme 4.12: Literature precedence for SN_2' reaction.

In addition to these strategies, a recent report by Szabó *et al.*,[111] has detailed a palladium catalysed allylic C-OH functionalisation for the synthesis of allylsilanes. Reactions were performed on tertiary allylic alcohol substrates similar to **182** used in

the present synthesis (Scheme 4.13). This work, could allow direct conversion of allylic alcohol **181** to the corresponding allylsilane, facilitating removal of a chemical step from the synthesis, as well as the use of highly toxic HMPA currently used when installing the silane portion of the molecule.



Scheme 4.13: Possible direct conversion to allylsilane **181**.

If the synthesis of popolohuanone E (**1**) was to be continued, improvements to the route could be made *via* the methods proposed above. This could allow the synthesis to be conducted in a more efficient manner and would reduce the number of steps towards the precursor to oxidative coupling, 6'-hydroxyarenarol (**7**). In addition, the results obtained in the dimerisation studies described in this thesis, provide promising evidence that with more time and material, the natural product popolohuanone E (**1**) could be synthesised *via* this route.

5.0 Experimental

5.1 General Experimental Details

For all non-aqueous chemistry, glassware was flame dried and reactions were carried out under an inert (N_2) atmosphere. For all air sensitive chemistry Schlenk glassware was flame dried under vacuum and reactions were carried out under a flow of argon. Cooling to 0 °C was affected using an ice-water bath. Cryogenic conditions (-78 °C) were achieved using a solid carbon dioxide-acetone bath. Degassing of solutions was conducted by freezing the solution using liquid N_2 and subjecting the flask to vacuum, followed by slowly warming to room temperature. This was repeated three times. For the purpose of thin layer chromatography, Polygram® SilG/UV_{254} 0.25 mm silica gel plates were used. Visualisation was achieved using ultraviolet light, (254nm) and/or anisaldehyde or $KMnO_4$ solutions as appropriate. Removal of solvents (*in vacuo*) was achieved using a water aspirator and Büchi rotary evaporators. Flash column chromatography was performed using Geduran® silica gel 60, 40-63 μm.

5.2 Analytical Instruments and Characterisation

All ^1H, ^{19}F and ^{13}C NMR data were recorded using Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz and Bruker AVANCE III 600 MHz. Data was manipulated directly using Bruker XwinNMR (version 2.6) or Topspin (version 2.1). Samples were made as dilute solutions of $CDCl_3$ unless otherwise stated. All chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. δ = 7.27 for ^1H NMR and δ = 77.2 for ^{13}C NMR in $CDCl_3$. Multiplicities for ^1H coupled signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Coupling constants (*J*) are reported in Hertz. Where a 1:1 mixture of diastereoisomers is observed the total number of assigned protons is equal to the total number of protons present in one molecule. ^{13}C multiplicities were assigned using a DEPT sequence. Where appropriate, HMQC, COSY, HMBC experiments were carried out to aid assignment.

Mass spectra were acquired on Thermo Finnigan Mat900xp **(**EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data was collected using Perkin-Elmer 1600 FTIR as dilute chloroform solutions or thin film. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Melting points are uncorrected and were recorded on a Stuart Scientific SMP3 system. Optical rotations were obtained using a Jasco DIP370 digital polarimeter and are reported in deg cm^2 g^{-1}.

5.3 Purification of Solvents and Reagents

Commercial solvents and reagents were used as supplied or purified in accordance with standard procedures.[112]

Dichloromethane (CH_2Cl_2) was obtained from a solvent tower, where degassed dichloromethane was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Diethyl ether (Et_2O) was obtained from a solvent tower, where degassed diethylether was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Diisopropylamine (*i*-Pr_2NH) was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

***N,N,N',N'*-tetramethylethylenediamine** (TMEDA) was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

Tetrahydrofuran (THF) was obtained from a solvent tower, where degassed tetrahydrofuran was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

Triethylamine (Et_3N) was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

Toluene was obtained from a solvent tower, where degassed toluene was passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure.

1,2,4-Trimethoxybenzene was distilled from calcium hydride powder under an atmosphere of nitrogen and stored in a darkened fridge.

Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over 4 Å molecular sieves.

All solutions of organolithium reagents were standardised with diphenyl acetic acid, or *N*-benzyl benzamide.

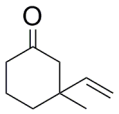
Activation of 4 Å molecular sieves was achieved by heating under high vacuum.

$Ph_3SiOReO_3$ was prepared according to a literature procedure.[113]

5.4 Experimental Procedures

5.4.1 Model System Studies

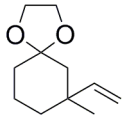
3-Methyl-3-vinyl-cyclohexanone (137)[76]



137

To a suspension of CuI (3.45 g, 18.1 mmol, 0.2 equiv.) in THF (385 mL) was added vinylmagnesium bromide (136 mL, 136 mmol of a 1.0 M sol. in THF, 1.5 equiv.) *via* cannula and the reaction stirred at –78 °C for 30 min. To the mixture was then added 3-methylcyclohexenone **136** (10.0 g, 90.8 mmol) in THF (45 mL) *via* cannula. The reaction was stirred at –78 °C for 1 h before being warmed to rt and stirred for a further 30 min. The reaction mixture was poured onto sat. aq. NH_4Cl (200 mL) and the layers separated. The aq. layer was extracted with Et_2O (100 mL) and the combined organics washed with brine (75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **137**. Purification by flash column chromatography (15% EtOAc/pet. ether) gave **137** (8.60 g, 69%, lit.[76] 64%) as a colourless oil; R_f 0.45 (15% EtOAc/pet. ether); ^{1}H NMR (400 MHz) δ 1.07 (3H, s, C*H*$_3$), 1.58-1.67 (1H, m, *Cy*), 1.70-1.78 (1H, m, *Cy*), 1.83-1.89 (2H, m, *Cy*), 2.18 (1H, d, *J* = 14.0, *Cy*), 2.22-2.37 (2H, m, *Cy*), 2.46 (1H, d, *J* = 14.0, *Cy*), 4.98 (1H, d, *J* = 17.6, CH=C*H*$_{trans}$H), 5.02 (1H, d, *J* = 10.8, CH=C*H*$_{cis}$H), 5.73 (1H, dd, *J* = 17.6, 10.8, C*H*=CH$_2$). Data in agreement with that reported.[76]

7-Methyl-7-vinyl-1,4-dioxa-spiro[4.5]decane (138)[76]

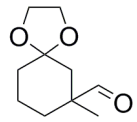


138

To a solution of ketone **137** (16.6 g, 120 mmol) in benzene (342 mL) was added 1,2-dihydroxyethane (7.30 mL, 132 mmol, 1.1 equiv.) and CSA (274 mg, 1.20 mmol, 1.0 mol%). The reaction was heated in Dean Stark apparatus for 18 h before being cooled to rt. The solvents were removed *in vacuo* to give crude **138** (21.8 g, 99%, lit.[76] 99%) as a colourless oil, which was used without purification; ^{1}H NMR (270 MHz), δ 1.08

(3H, s, CH_3), 1.29-1.38 (1H, m, *Cy*), 1.44-1.70 (7H, m, *Cy*), 3.89-3.98 (4H, m, OCH_2CH_2O), 4.90 (1H, dd, J = 11.2, 1.2, CH=CH_{cis}H), 4.94 (1H, dd, J = 18.0, 1.8, CH=CH_{trans}H), 5.94 (1H, dd, J = 17.6, 10.8, CH=CH_2). Data in agreement with that reported.[76]

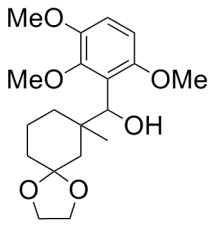
7-Methyl-7-carbaldehyde-1,4-dioxa-spiro[4.5]decane (139)[76]



139

To a solution of olefin **138** (21.8 g, 120 mmol) in Me_2CO:H_2O (3.2:1, 420 mL) at rt was added OsO_4 (127 mg, 480 μmol, 0.4 mol%), NMO (17.6 g, 150 mmol, 1.3 equiv.) and quinuclidine (13.8 mg, 2.40 mmol, 2.0 mol%). The reaction was stirred for 19 h, after which $NaIO_4$ (25.6 g, 120 mmol, 1.0 equiv.) was added and the reaction stirred for a further 17 h. To the mixture was added Et_2O (100 mL) and the layers separated. The aq. layer was extracted with Et_2O (2 x 70 mL) and the combined organics were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **139**. Purification by flash column chromatography (20% EtOAc/pet. ether) gave **139** (16.0 g, 72%, lit.[76] 84%) as a colourless oil; R_f 0.44 (20% EtOAc/pet. ether); ^{1}H NMR (400 MHz) δ 1.00 (3H, s, CH_3), 1.10-1.20 (1H, m, *Cy*), 1.42-1.52 (2H, m, *Cy*), 1.61-1.70 (3H, m, *Cy*), 2.04 (1H, d, J = 16.2, *Cy*), 2.10 (1H, d, J = 16.2, *Cy*), 3.82-4.03 (4H, m, OCH_2CH_2O), 9.45 (1H, d, J = 1.2, CHO). Data in agreement with that reported.[76]

(7-Methyl-1,4-dioxa-spiro[4.5]dec-7-yl)-(2,3,6-trimethoxyphenyl)-methanol (140)[76]

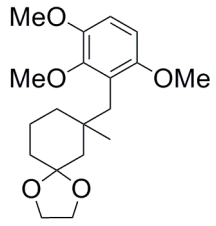


140

To a solution of 1,2,4-trimethoxybenzene (24.6 mL, 165 mmol, 3.0 equiv.) in THF (300 mL) at 0 °C under N_2 was added TMEDA (49.8 mL, 330 mmol, 6.0 equiv.) and *n*-butyllithium (66.1 mL, 165 mmol of a 2.5 M sol. in hexanes, 3.0 equiv.). The

reaction was stirred at 0 °C for 30 min before being cooled to –78 °C. To the solution was added aldehyde **139** (10.2 g, 55.0 mmol) in THF (25 mL) *via* cannula and the reaction stirred for 30 min at –78 °C before being warmed to rt and stirred for a further 30 min. The reaction was diluted with H_2O (150 mL) and 1 M HCl (150 mL) and the layers separated. The aq. layer was extracted with Et_2O (150 mL) and the combined organics washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **140**. Purification by flash column chromatography (20% EtOAc/pet. ether) gave **140** (17.7 g, 91%, lit.[76] 91%) as a yellow oil as an inseparable 4:1 mixture of diastereoisomers (some signals split by atropisomerism between Ar-CHOH bond); R_f 0.16 (20% EtOAc/pet. ether); ^{1}H NMR (300 MHz) (asterix denotes signals due to minor diastereosiomer) δ 1.00* (3H, s, C*H*$_3$), 1.01 (3H, s, C*H*$_3$), 1.10-1.75 (8H, m, *Cy*), 3.78-3.84 (9H, m, 3 x OC*H*$_3$), 3.85-3.98 (4H, m, OC*H*$_2$C*H*$_2$O), 4.27* (1H, d, *J* = 12.0, ArC*H*OH), 4.41 (1H, d, *J* = 11.4, ArC*H*OH), 4.78 (1H, d, *J* = 12.0, ArCHO*H*), 4.94* (1H, d, *J* = 12.0, ArCHO*H*), 6.53* (1H, d, *J* = 9.0, Ar*H*), 6.59 (1H, d, *J* = 9.0, Ar*H*), 6.78 (1H, d, *J* = 9.0, Ar*H*). Data in agreement with that reported.[76]

7-Methyl-7-(2,3,6-trimethoxybenzyl)-1,4-dioxa-spiro[4.5]decane (142)[76]

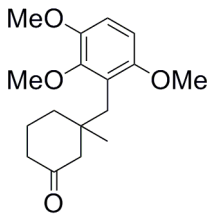


142

To a solution of alcohol **140** (19.8 g, 56.3 mmol) in THF (500 mL) at –78 °C under N_2 was added $NaN(TMS)_2$ (85.2 mL, 170 mmol of a 2.0 M sol. in THF, 3.0 equiv.). The reaction was stirred for 30 min at –78 °C before CS_2 (21.5 mL, 357 mmol, 6.5 equiv.) was added and the reaction warmed to –55 °C over 1 h. The reaction was re-cooled to –78 °C, before CH_3I (11.8 mL, 187 mmol, 3.5 equiv.) was added and the reaction mixture warmed to –55 °C over 1 h. Sat. aq. $Na_2S_2O_3$ (400 mL) was added and the reaction mixture warmed to rt before the layers were separated. The aq. layer was extracted with Et_2O (3 x 200 mL) and the combined organics washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude xanthate **141** (24.0 g, 97%, lit.[76] 94%) as a yellow oil, which was used without purification.

To a solution of crude xanthate **141** (24.0 g, 54.2 mmol) in toluene (280 mL) under an argon atmosphere was added Bu_3SnH (64.2 mL, 244 mmol, 4.5 equiv.) and AIBN (888 mg, 5.42 mmol, 10 mol%) and the reaction mixture was degassed. The reaction was heated at reflux for 2 h before being cooled and concentrated *in vacuo* to give crude **142**. Purification by flash column chromatography (15% EtOAc/pet. ether) gave **142** (14.7 g, 81%, lit.[76] 80%) as a colourless oil; R_f 0.25 (15% EtOAc/pet. ether); ^{1}H NMR (400 MHz) δ 0.97 (3H, s, C*H*$_3$), 1.23-1.70 (8H, m, *Cy*), 2.55 (1H, d, *J* = 12.8, C*H*$_2$Ar), 2.75 (1H, d, *J* = 12.8, C*H*$_2$Ar), 3.74 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.88-3.95 (4H, m, OC*H*$_2$C*H*$_2$O), 6.54 (1H, d, *J* = 8.8, Ar*H*), 6.73 (1H, d, *J* = 8.8, Ar*H*). Data in agreement with that reported.[76]

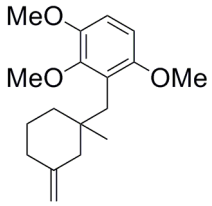
3-Methyl-3-(2,3,6-trimethoxybenzyl)-cyclohexanone (143)[76]



143

To a solution of acetal **142** (14.7 g, 43.8 mmol) in Me_2CO:H_2O (1:1, 500 mL) was added conc. HCl (1.27 mL) and the reaction was stirred for 36 h before being diluted with EtOAc (100 mL). The layers were separated and the organic layer washed with 0.1 M NaOH (150 mL). The aq. layer was extracted with EtOAc (2 x 200 mL) and the combined organics washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **143**. Purification by flash column chromatography (25% EtOAc/Pet. ether) gave **143** (10.6 g, 83%, lit.[76] 93%) as a colourless oil; R_f 0.35 (25% EtOAc/Pet. ether); ^{1}H NMR (400 MHz), δ 0.92 (3H, s, C*H*$_3$), 1.60-1.71 (2H, m, *Cy*), 1.74-1.86 (1H, m, *Cy*), 1.90-1.99 (1H, m, *Cy*), 2.11 (1H, dt, *J* = 13.6, 2.0, *Cy*), 2.14-2.27 (2H, m, *Cy*), 2.30 (1H, d, *J* = 14.0, *Cy*), 2.67 (1H, d, *J* = 12.4, C*H*$_2$Ar), 2.71 (1H, d, *J* = 12.4, C*H*$_2$Ar), 3.74 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 6.56 (1H, d, *J* = 8.8, Ar*H*), 6.76 (1H, d, *J* = 9.2, Ar*H*). Data in agreement with that reported.[76]

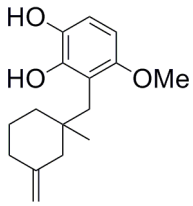
1,2,4-Trimethoxy-3-(1-methyl-3-methylene-cyclohexylmethyl)-benzene (144)[76]



144

To a suspension of methyltriphenylphosphonium bromide (2.20 g, 6.20 mmol, 1.2 equiv.) in Et_2O (212 mL) at 0 °C under N_2 was added *n*-butyllithium (2.48 mL, 6.20 mmol of a 2.5 M sol. in hexanes, 1.2 equiv.). The mixture was stirred at 0 °C for 1 h before ketone **143** (1.50 g, 5.14 mmol) was added as a solution in Et_2O (30 mL). The reaction was stirred for a further 30 min before H_2O (70 mL) was added and the layers separated. The aq. layer was extracted with Et_2O (2 x 75 mL) and the combined organics washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude alkene **144**. Purification by flash column chromatography (20% EtOAc/pet. ether) gave **144** (900 mg, 60%, lit.[76] 78%) as a colourless oil; R_f 0.72 (20% EtOAc/pet. ether); ^{1}H NMR (400 MHz) δ 0.81 (3H, s, C*H*$_3$), 1.39-1.56 (3H, m, *Cy*), 1.59-1.69 (1H, m, *Cy*), 1.93 (2H, app. d, *J* = 12.8, *Cy*), 2.08 (1H, d, *J* = 13.2, *Cy*), 2.15 (1H, dt, *J* = 13.2, 4.0, *Cy*), 2.59 (1H, d, *J* = 12.4, C*H*$_2$Ar), 2.65 (1H, d, *J* = 12.8, C*H*$_2$Ar), 3.74 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 4.55 (1H, s, C=C*H*$_2$), 4.64 (1H, s, C=C*H*$_2$), 6.56 (1H, d, *J* = 8.8, Ar*H*), 6.74 (1H, d, *J* = 8.8, Ar*H*). Data in agreement with that reported.[76]

4-Methoxy-3-(1-methyl-3-methylene-cyclohexylmethyl)-benzene-1,2-diol (215)[79]

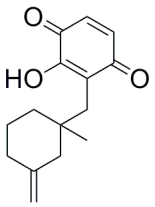


215

To a solution of diphenylphosphine (14.2 mL, 81.4 mmol, 20.0 equiv.) in THF (120 mL) at 0 °C under N_2 was added *n*-butyllithium (29.3 mL, 73.2 mmol as a 2.5 M sol. in hexanes, 18.0 equiv.) dropwise. The reaction was stirred at rt for 30 min after which time arene **144** (1.18 g, 4.07 mmol) in THF (10 mL) was added *via* cannula. The reaction mixture was heated at reflux for 18 h before being allowed to cool to rt and H_2O (40 mL) added. The layers were separated and the aq. layer extracted with

Et_2O (30 mL). The combined organics were washed with H_2O (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **215**. Purification by flash column chromatography (20% EtOAc/pet. ether) gave diol **215** (620 mg, 58%, lit.[79] 90%) as a colourless oil; R_f 0.36 (20% EtOAc/pet. ether); ^1H NMR (400 MHz) δ 0.87 (3H, s, C*H*$_3$), 1.46-1.53 (3H, m, *Cy*), 1.62-1.70 (1H, m, *Cy*), 1.97 (1H, d, *J* = 13.2, *Cy*), 2.10-2.31 (1H, m, *Cy*), 2.12 (1H, d, *J* = 13.2, *Cy*), 2.15-2.22 (1H, m, *Cy*), 2.61 (1H, d, *J* = 13.2, C*H*$_2$Ar), 2.67 (1H, d, *J* = 13.2, C*H*$_2$Ar), 3.73 (3H, s, OC*H*$_3$), 4.61 (1H, d, *J* = 1.2, C=C*H*$_2$), 4.71 (1H, d, *J* = 1.5, C=C*H*$_2$), 6.33 (1H, d, *J* = 12.0, Ar*H*), 6.72 (1H, d, *J* = 11.6, Ar*H*). Data in agreement with that reported.[79]

2-Hydroxy-3-(1-methyl-3-methylene-cyclohexylmethyl)-[1,4]-benzoquinone (216)[79]

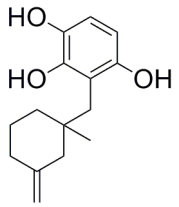


216

A solution of CAN (1.09 g, 1.99 mmol, 2.5 equiv.) in MeCN:H_2O (2:1, 23 mL) was added fast dropwise to diol **215** (210 mg, 820 μmol) in MeCN:H_2O (2:1, 23 mL) at 0 °C. The solution immediately turned dark red and TLC analysis after 5 min showed complete consumption of starting material to an orange spot (R_f = 0.35, 30% EtOAc/pet. ether) (*ortho*-quinone). After a further 30 min the reaction was warmed to rt and stirred for a further 2 h until the solution had lightened to yellow and TLC analysis showed complete conversion to a new yellow spot (R_f = 0.69, 30% EtOAc/pet. ether). To the solution was added H_2O (30 mL) and Et_2O (30 mL) and the layers separated. The aq. phase was extracted with Et_2O (3 x 30 mL) and the combined organics washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **216** (190 mg, 95% as a crude mixture, lit.[79] 66% after purification) as a low melting orange solid; mp. 28-32 °C, (no lit. mp. reported) which was used without purification; R_f 0.69 (30% EtOAc/pet. ether); ^1H NMR (400 MHz) δ 0.83 (3H, s, C*H*$_3$), 1.08-1.39 (2H, m, *Cy*), 1.45-1.54 (1H, m, *Cy*), 1.66-1.70 (1H, m, *Cy*), 1.90-2.05 (3H, m, *Cy*), 1.12-2.19 (1H, m, *Cy*), 2.42 (1H, d, *J* = 12.8, C*H*$_2$Ar), 2.50 (1H, d, *J* = 12.8, C*H*$_2$Ar), 4.58 (1H, s, C=C*H*$_2$), 4.68 (1H, s, C=C*H*$_2$),

6.75 (1H, d, *J* = 10.0, Ar*H*), 6.78 (1H, d, *J* = 9.6, Ar*H*). Data in agreement with that reported.[79]

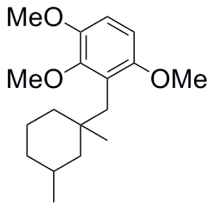
3-(1-Methyl-3-methylene-cyclohexylmethyl)-benzene-1,2,4-triol (110)[79]



110

To a solution of quinone **216** (690 mg, 2.80 mmol, 2.5 equiv.) in Et_2O (100 mL) was added a solution of $Na_2S_2O_4$ (2.00 g) in H_2O (100 mL). The mixture was shaken in a separating funnel for 10 min until the organic layer had turned from yellow to colourless and TLC analysis showed complete consumption of starting material. The layers were separated and the organic layer was washed with H_2O (70 mL), brine (70 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo* to give crude **110**. Purification by flash column chromatography (25% EtOAc/pet. ether) gave triol **110** (300 mg, 51% from diol **215**, lit.[79] 55%) as a yellow oil; R_f 0.35 (25% EtOAc/pet. ether); ^{1}H NMR (400 MHz) δ 0.92 (3H, s, C*H*$_3$), 1.42-1.62 (3H, m, *Cy*), 1.64-1.72 (1H, m, *Cy*), 1.96-2.06 (2H, m, *Cy*), 2.12-2.19 (2H, m, *Cy*), 2.58 (1H, d, *J* = 14.0, C*H*$_2$Ar), 2.63 (1H, d, *J* = 14.0, C*H*$_2$Ar), 4.63 (2H, m, CH=C*H*$_2$ + O*H*), 4.73 (1H, s, CH=C*H*$_2$), 5.04 (1H, br s, O*H*), 5.74 (1H, br s, O*H*), 6.27 (1H, d, *J* = 8.4, Ar*H*), 6.63 (1H, d, *J* = 9.2, Ar*H*). Data in agreement with that reported.[79]

3-(1,3-Dimethyl-cyclohexylmethyl)-1,2,4,trimethoxy-benzene (145)

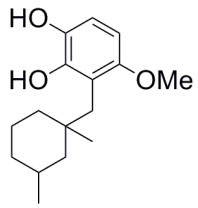


145

To a solution of trimethylated arene **144** (0.60 g, 2.1 mmol) in MeOH (30 mL) was added 10% palladium on carbon (60 mg, 0.1 equiv. by weight). A triple evacuation/H_2 fill was then carried out. The mixture was stirred at rt and pressure for 36 h. During this time a further H_2 refill and triple evacuation was carried out. The mixture was then filtered through celite® washed with MeOH (10 mL), H_2O (10 mL)

and concentrated *in vacuo* to give crude **145** (0.52 g, 86%) as a colourless oil as an inseparable 1:1 mixture of diastereoisomers; R_f 0.70 (20% EtOAc/pet. ether); IR υ_{max} (solution in $CHCl_3$) 3055 (CH), 3046 (CH), 1602, 1462, 1326 cm^{-1}; ^1H NMR (300 MHz) δ 0.63-0.70 (0.5H, m, C*H*CH_3), 0.71 (1.5H, s, C*H*$_3$), 0.81 (1.5H, d, *J* = 6.4, C*H*$_3$), 0.88 (1.5H, d, *J* = 6.4, C*H*$_3$), 0.89 (1.5H, s, C*H*$_3$), 0.91-1.20 (0.5H, m, C*H*CH_3), 1.28-1.33 (0.5H, m, *Cy*), 1.35-1.41 (1.5H, m, *Cy*), 1.42-1.52 (1H, m, *Cy*), 1.52-1.62 (3.5H, m, *Cy*), 1.66-1.90 (1.5H, m, *Cy*), 2.56 (1H, s, C*H*$_2$Ar), 2.68 (1H, s, C*H*$_2$Ar), 3.74 (3H, s, OC*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 6.53 (0.5H, d, *J* = 5.4, Ar*H*), 6.66 (0.5H, d, *J* = 5.4, Ar*H*), 6.72 (0.5H, d, *J* = 1.8, Ar*H*), 6.74 (0.5H, d, *J* = 2.1, Ar*H*); ^{13}C NMR (100 MHz) δ 22.7 (*C*H_2), 22.8 (*C*H_3), 23.4 (*C*H_3), 23.4 (*C*H_3), 28.3 (*C*H), 28.3 (*C*H), 29.7 (*C*H_3), 30.2 (*C*H_2), 35.5 (*C*H_2), 35.6 (*C*H_2), 36.1 (2 x Cq), 36.9 (*C*H_2), 37.2 (*C*H_2), 38.9 (*C*H_2), 39.0 (*C*H_2), 47.1 (*C*H_2), 48.7 (*C*H_2), 55.4 (O*C*H_3), 55.6 (O*C*H_3), 56.2 (2 x O*C*H_3), 60.2, (O*C*H_3), 60.3 (O*C*H_3), 104.8 (Ar), 105.1 (Ar), 109.8 (Ar), 109.9 (Ar), 122.7 (Cq), 123.8 (Cq), 147.1 (2 x Cq), 149.3 (2 x Cq), 153.2 (Cq), 153.3 (Cq); *m/z* (ESI^+) 315 (100%, MNa^+), 293 (27%, MH^+); HRMS: found 315.1929, $C_{18}H_{28}O_3Na$ requires 315.2931; Anal. Cald. For $C_{18}H_{28}O_3$: C, 73.93, H, 9.65. Found C, 74.06, H, 9.60%.

3-(1,3-Dimethyl-cyclohexylmethyl)-4-methoxybenzene-1,2-diol (146)

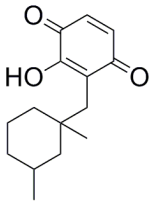


146

To a solution of diphenylphosphine (22.6 mL, 128 mmol, 20.0 equiv.) in THF (250 mL) at 0 °C under N_2 was added *n*-butyllithium (46.4 mL, 115 mmol as a 2.5 M sol. in hexanes, 18.0 equiv.) dropwise. The reaction was stirred at rt for 30 min after which time arene **145** (1.88 g, 6.44 mmol) in THF (55 mL) was added *via* cannula. The reaction mixture was heated at reflux for 18 h before being allowed to cool to rt and H_2O (100 mL) added. The layers were separated and the aq. layer extracted with Et_2O (100 mL). The combined organics were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **146**. Purification by flash column chromatography (20% EtOAc/pet. ether) gave diol **146** (1.45 g, 86%) as a colourless oil as an inseparable 1:1 mixture of diastereoisomers; R_f

0.36 (20% EtOAc/pet. ether); IR υ_{max} (solution in $CHCl_3$) 3691 (OH), 3604 (OH), 2925 (CH), 1602, 1491, 1485 cm^{-1}; ^1H NMR (400 MHz) δ 0.66-0.78 (0.5H, m, C*H*), 0.79 (1.5H, s, CH_3), 0.83 (1.5H, d, *J* = 6.4, CH_3) 0.88 (1.5H, d, *J* = 6.4, CH_3), 0.94 (1.5H, s, CH_3), 0.96-1.06 (0.5H, m, C*H*), 1.17-1.30 (1.5H, m, *Cy*), 1.35-1.45 (1.5H, m, *Cy*), 1.46-1.66 (3.5H, m, *Cy*), 1.67-1.79 (1H, m, *Cy*), 1.79-1.94 (0.5H, m, *Cy*), 2.57 (1H, s, CH_2Ar), 2.66 (0.5H, d, *J* = 13.2, CH_2Ar), 2.73 (0.5H, d, *J* = 13.2, CH_2Ar), 3.72 (1.5H, s, OCH_3), 3.73 (1.5H, s, OCH_3) 6.29 (0.5H, d, *J* = 8.4, Ar*H*), 6.33 (0.5H, d, *J* = 8.8, Ar*H*), 6.69 (0.5H, d, *J* = 8.8, Ar*H*), 6.70 (0.5H, d, *J* = 8.4, Ar*H*); ^{13}C NMR (100 MHz) δ 21.3 (*C*H_3), 22.5 (*C*H_2), 22.8 (*C*H_2), 23.3 (*C*H_3), 28.2 (*C*H), 28.3 (*C*H), 30.0 (*C*H_3), 30.1 (*C*H_3), 35.5 (*C*H_2), 35.6 (CH_2), 36.2 (Cq), 37.2 (*C*H_2), 38.9 (*C*H_2), 39.0 (*C*H_2), 47.0 (*C*H_2), 48.2 (*C*H_2), 55.4 (O*C*H_3), 55.7 (O*C*H_3), 60.8 (*C*H_2), 101.5 (Ar), 102.1 (Ar), 112.3 (Ar), 112.3 (Ar), 115.3 (Cq), 116.3 (Cq), 137.3 (Cq), 137.7 (Cq), 143.8 (Cq), 144.3 (Cq), 153.4 (Cq), 153.4 (Cq), one quaternary carbon could not be distingushed; *m/z* (ESI^+) 287 (100%, MNa^+), 265 (5%, MH^+); HRMS: found 287.1615, $C_{16}H_{24}O_3Na$ requires 287.1623; Anal. Cald. For $C_{16}H_{24}O_3$: C, 72.69, H, 9.15. Found C, 72.42, H, 9.24%.

3-(1,3-Dimethyl-cyclohexylmethyl)-2-hydroxy-[1,4]-benzoquinone (147)

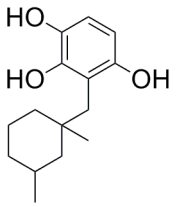


147

A solution of CAN (7.57 g, 13.8 mmol, 2.5 equiv.) in MeCN:H_2O (2:1, 200 mL) was added fast dropwise to diol **146** (1.45 g, 5.51 mmol) in MeCN:H_2O (2:1, 200 mL) at 0 °C. The solution immediately turned red and TLC analysis after 5 min showed complete consumption of starting material to an orange spot (R_f = 0.23, 20% EtOAc/Pet. ether) (*ortho*-quinone). After a further 30 min the reaction was warmed to rt and stirred for a further 2 h until the solution had become yellow and TLC analysis showed complete conversion to a new yellow spot (R_f = 0.73). To the solution was added H_2O (30 mL) and Et_2O (30 mL) and the layers were separated. The aq. phase was extracted with Et_2O (2 x 30 mL) and the combined organics washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **147**. Purification by flash column chromatography (20% EtOAc/Pet. ether) gave

quinone **147** (0.88 g, 64%) as a yellow oil, as an inseparable 1:1 mixture of diastereoisomers; R_f 0.73 (20% EtOAc/pet. ether); IR υ_{max} (solution in $CHCl_3$) 3420 (OH), 2925 (CH), 1668 (C=O), 1644 (C=O), 1386, 1352 cm^{-1}; ^1H NMR (400 MHz) δ 0.70-0.75 (0.5H, m, C*H*), 0.73 (1.5H, s, CH_3), 0.85 (1.5H, d, *J* = 6.4, CH_3), 0.86 (1.5H, d, *J* = 6.4, CH_3), 0.92 (1.5H, s, CH_3), 1.01 (0.5H, td, *J* = 13.6, 4.4, *Cy*), 1.15 (0.5H, td, *J* = 13.0, 4.4, *Cy*), 1.25-1.63 (0.5H, m, C*H*, + 5.5H, m, *Cy*), 1.64-1.73 (1H, m, *Cy*), 1.78-1.85 (0.5H, m, *Cy*), 2.40 (1H, s, CH_2Ar), 2.54 (1H, s, CH_2Ar), 6.74 (1H, dd, *J* = 10.0, 1.6, Ar*H*), 6.77 (1H, d, *J* = 10.0, 1.6, Ar*H*), 6.91 (0.5H, s, O*H*), 6.92 (0.5H, s, O*H*); ^{13}C NMR (100 MHz) δ 22.4 (*C*H_2), 23.2 (2 x *C*H_3), 23.3 (*C*H_3), 28.0 (*C*H), 28.2 (*C*H), 29.4 (*C*H_2), 30.7 (*C*H_3), 35.2 (*C*H_2), 35.4 (*C*H_2), 36.6 (Cq), 37.3 (Cq), 37.7 (*C*H_2), 38.0 (*C*H_2), 38.7 (*C*H_2), 47.3 (*C*H_2), 48.1 (*C*H_2), 120.0 (Cq), 121.1 (Cq), 131.7 (Ar), 131.7 (Ar), 139.5 (Ar), 139.6 (Ar), 152.5 (Cq), 152.5 (Cq), 183.1 (C=O), 183.2 (C=O), 188.1 (C=O), 188.1 (C=O), one CH_2 could not be distinguished; *m/z* (ESI^+) 271 (100%, MNa^+), 249 (9%, MH^+); HRMS: found 271.1305, $C_{15}H_{20}O_3Na$ requires 271.1310; Anal. Cald. For $C_{15}H_{20}O_3$: C, 72.55, H, 8.12. Found C, 72.65, H, 8.21%.

3-(1,3-Dimethyl-cyclohexylmethyl)-benzene-1,2,4-triol (132)

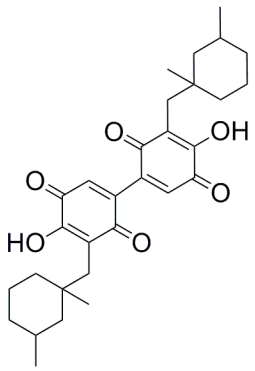


132

To a solution of quinone **147** (139 mg, 560 μmol) in Et_2O (80 mL) was added a solution of $Na_2S_2O_4$ (2.00 g) in H_2O (80 mL). The mixture was shaken in a separating funnel for 10 min until the organic layer had turned from yellow to colourless and TLC analysis showed complete consumption of starting material. The layers were separated and the organic layer was washed with H_2O (70 mL), brine (70 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **132**. Purification by flash column chromatography (20% EtOAc/pet. ether) gave triol **132** (113 mg, 60%) as a yellow oil, as an inseparable 1:1 mixture of diastereoisomers; R_f 0.19 (20% EtOAc/pet. ether); IR υ_{max} (solution in $CHCl_3$) 3692 (OH), 3604 (OH), 3549 (OH), 2951 (CH), 2925 (CH), 1487, 1459 cm^{-1}; ^1H NMR (400 MHz) δ 0.70-0.80 (0.5H, m,

C*H*), 0.85 (1.5H, d, *J* = 6.0, C*H*$_3$), 0.86 (1.5H, s, C*H*$_3$), 0.89 (1.5H, d, *J* = 6.0, C*H*$_3$), 1.00 (1.5H, s, C*H*$_3$), 1.01-1.09 (0.5H, m, C*H*), 1.18-1.28 (1H, m, *Cy*), 1.39-1.47 (2H, m, *Cy*), 1.48-1.56 (2H, m, *Cy*), 1.57-1.65 (2H, m, *Cy*), 1.68-1.79 (0.5H, m, *Cy*), 1.79-1.90 (0.5H, m, *Cy*), 2.54 (1H, s, C*H*$_2$Ar), 2.68 (1H, s, C*H*$_2$Ar), 6.21 (0.5H, d, *J* = 8.4, Ar*H*), 6.26 (0.5H, d, *J* = 8.4, Ar*H*), 6.57 (0.5H, d, *J* = 8.8, Ar*H*), 6.58 (0.5H, d, *J* = 8.4, Ar*H*); ^{13}C NMR (100 MHz) δ 22.4 (*C*H$_2$), 22.8 (*C*H$_2$), 22.9 (*C*H$_3$), 23.3 (*C*H$_3$), 23.3 (*C*H$_3$), 28.3 (*C*H), 28.5 (*C*H), 30.0 (*C*H$_3$), 30.5 (*C*H$_2$), 35.3 (*C*H$_2$), 35.4 (*C*H$_2$), 36.4 (Cq), 37.2 (*C*H$_2$), 37.4 (Cq), 38.7 (*C*H$_2$), 39.4 (*C*H$_2$), 46.9 (*C*H$_2$), 48.3 (*C*H$_2$), 106.1 (Ar), 106.5 (Ar), 113.2 (Ar), 113.3 (Ar), 113.5 (Cq), 114.7 (Cq), 136.8 (Cq), 137.1 (Cq), 144.2 (Cq), 144.6 (Cq), 149.3 (Cq), 149.5 (Cq); *m/z* (ESI$^-$) 249 (100%, M$^+$-H$^-$); HRMS: found 249.1497, $C_{15}H_{21}O_3$ requires 249.1491; Anal. Cald. For $C_{15}H_{22}O_3$: C, 71.97, H, 8.86. Found C, 71.59, H, 9.15%.

3,3'-Bis-(1,3-dimethyl-cyclohexylmethyl)-4,4'-dihydroxy-bicyclohexyl-3,6,3',6'-tetraene-2,5,2',5' tetraone (133)

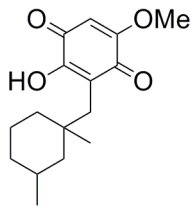


133

To a degassed suspension of $FeCl_3$ (10.3 g, 2.74 mmol, 5% by weight on SiO_2, 8.0 equiv.) in H_2O (17 mL) was added a degassed solution of triol **132** (100 mg, 340 μmol), in MeOH:H_2O (2:1, 3 mL) *via* cannula. The solution immediately turned dark brown and was stirred for 5 min before being filtered and washed with Et_2O (40 mL). The layers were separated and the aq. layer was extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **133**. Purification by flash column chromatography (20-40% EtOAc/hexanes) gave bis-quinone **133** (35 mg, 35%) as an orange oil, as an inseparable mixture of diastereoisomers; R_f 0.45 (40% EtOAc/hexanes); IR υ_{max} (solution in $CHCl_3$) 3422 (OH), 3011 (CH), 2927 (CH), 2855 (CH), 1723 (C=O), 1655 (C=O), 1603 (C=C), 1459, 1381, 1288 (C-O) cm^{-1}; ^{1}H

NMR (400 MHz) δ 0.70-0.78 (3H, m, *Cy*), 0.79 (1.5H, s, CC*H*$_3$), 0.80 (1.5H, s, CC*H*$_3$), 0.85 (6H, d, *J* = 6.4, 2 x CHC*H*$_3$), 0.91 (3H, s, CC*H*$_3$), 0.95-1.08 (1H, m, *Cy*), 1.15 (1H, td, *J* = 13.2, 4.4, *Cy*), 1.33-1.40 (3H, m, *Cy*), 1.42-1.66 (6H, m, 2C*H* + 4*Cy*), 1.60-1.85 (4H, m, *Cy*), 2.42 (2H, s, ArC*H*$_2$), 2.57 (2H, m, ArC*H*$_2$), 6.74 (1H, s, Ar*H*), 6.75 (1H, s, Ar*H*), 6.96 (2H, s, O*H*); ^{13}C NMR (100 MHz) δ 22.2 (*C*H$_2$), 22.9 (*C*H$_2$), 23.0 (*C*H$_3$), 23.1 (*C*H$_3$), 27.8 (*C*H), 28.0 (*C*H), 29.5 (*C*H$_2$), 29.5 (*C*H$_2$), 30.6 (*C*H$_3$), 30.7 (*C*H$_3$), 35.0 (*C*H$_2$), 35.2 (*C*H$_2$), 36.6 (Cq), 36.9 (Cq), 37.6 (*C*H$_2$), 38.3 (*C*H$_2$), 47.1 (*C*H$_2$), 48.1 (*C*H$_2$), 120.6 (Cq), 121.7 (Cq), 130.4 (Ar), 130.4 (Ar), 144.2 (Cq), 144.4 (Cq), 152.3 (Cq), 152.3 (Cq), 182.0 (C=O), 182.1 (C=O), 185.5 (C=O), 185.5 (C=O); *m/z* (ESI$^-$) 493 (100% M$^+$-H$^-$); HRMS: found 493.2605, $C_{30}H_{37}O_6$ requires 493.2596.

3-(1,3-Dimethyl-cyclohexylmethyl)-2-hydroxy-5-methoxy-[1,4]-benzoquinone (154)

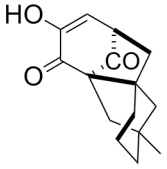


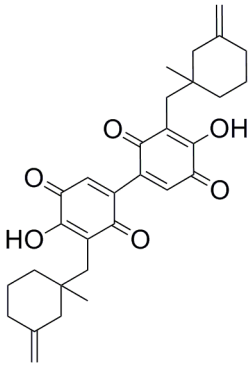
154

To a degassed suspension of $FeCl_3$ (9.30 g, 2.88 mmol, 5% by weight on SiO_2, 8.0 equiv.) in MeOH (9 mL) was added a degassed solution a triol **132** (90.0 mg, 360 μmol) in MeOH (3 mL) *via* cannula. The mixture immediately turned dark brown and was stirred for 5 min before being filtered and the solvents removed *in vacuo* to give crude **154**. Purification by flash column chromatography (40% EtOAc/pet. ether) gave quinone **154** (20.0 mg, 20%) as an orange oil, as an inseparable 1:1 mixture of diastereoisomers; R_f 0.40 (40% EtOAc/pet. ether); IR υ_{max} (solution in $CHCl_3$) 3381 (OH), 2927 (CH), 1645 (C=O), 1610 (C=O), 1457, 1389, 1353, 1240 (C-O) cm^{-1}; ^{1}H NMR (400 MHz) δ 0.67-0.75 (0.5H, m, C*H*), 0.76 (1.5H, s, C*H*$_3$), 0.82 (1.5H, d, *J* = 6.8, C*H*$_3$), 0.85 (1.5H, d, *J* = 6.4, C*H*$_3$), 0.90 (1.5H, s, C*H*$_3$), 0.93-1.04 (0.5H, m, *Cy*), 1.09-1.20 (0.5H, m, *Cy*), 1.23-1.39 (1.5H, m, *Cy*), 1.40-1.57 (5H, m, 4Cy + 0.5C*H*), 1.58-1.76 (1H, m, *Cy*), 1.78-1.86 (0.5H, m, *Cy*), 2.39 (1H, s, C*H*$_2$Ar), 2.53 (1H, s, C*H*$_2$Ar), 3.87 (3H, s, OC*H*$_3$), 5.86 (1H, s, Ar*H*), 7.36 (1H, br s, O*H*); ^{13}C NMR (100 MHz) δ 22.2 (*C*H$_2$), 22.9 (*C*H$_3$), 23.1 (*C*H$_3$), 27.8 (*C*H), 28.4

(*C*H), 29.4 (Ar*C*H$_2$), 29.7 (*C*H$_2$), 30.4 (2 x *C*H$_3$), 35.1 (*C*H$_2$), 35.2 (*C*H$_2$), 36.2 (Cq), 37.0 (Cq), 37.5 (*C*H$_2$), 37.7 (Ar*C*H$_2$), 38.4 (*C*H$_2$), 47.0 (*C*H$_2$), 47.9 (*C*H$_2$), 56.8 (2 x O*C*H$_3$), 102.1 (Ar), 102.1 (Ar), 116.8 (Cq), 117.9 (Cq), 152.9 (2 x Cq), 161.4 (2 x Cq), 182.2 (C=O), 182.4 (C=O), 182.7 (C=O), 182.7 (C=O); *m/z* (ESI$^+$) 301 (100%, MNa$^+$), 279 (9%, MH$^+$); HRMS: found 296.1858, $C_{16}H_{26}NO_4$ requires 296.1856, found 301.1399, $C_{16}H_{22}NaO_4$ requires 301.1410.

[5+2] Cycloaddition product (111)[79] and 3,3',-bis-(1-methyl-3-methylene-cyclohexylmethyl)- 4,4'-dihydroxy-bicyclohexyl-3,6,3',6'-tetraene-2,5,2',5' tetraone (155)



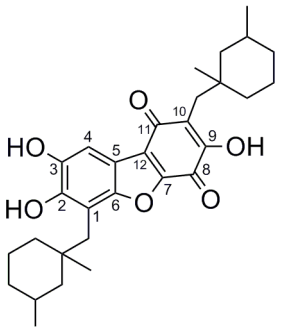


111 **155**

To a degassed suspension of $FeCl_3$ (9.40 g, 2.92 mmol, 5% by weight on SiO_2, 8 equiv.) in H_2O (14 mL) was added a degassed solution of triol **110** (90.0 mg, 363 μmol) in MeOH:H_2O (2:1, 3 mL) *via* cannula. The solution immediately turned dark brown and was stirred for 5 min before being filtered and washed with Et_2O (40 mL). The layers were separated and the aq. phase extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-40% EtOAc/hexanes) gave in order of elution, cycloaddition product **111** (35 mg, 39%, lit.[79] 86%) as a low melting colourless solid; mp. ~30 °C (no lit. mp. reported); R_f 0.24 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 1.07 (3H, s, C*H*$_3$), 1.21-1.38 (4H, m, *Cy*), 1.43-1.60 (4H, m, *Cy*), 1.68-1.85 (1H, m, C*H*$_2$), 2.00 (1H, d, *J* = 13.6, C*H*$_2$), 2.08 (1H, dd, *J* = 12.4, 6.8, C*H*$_2$), 2.38 (1H, d, *J* = 14.0, C*H*$_2$), 3.42 (1H, app. t, *J* = 7.4, COC*H*), 6.10 (1H, s, O*H*), 6.63 (1H, d, *J* = 8.4, C=C*H*). Data in agreement with that reported,[79] and bis-quinone **155** (5 mg, 6%) as a orange oil; R_f 0.48 (40% EtOAc/hexanes); IR υ_{max} (solution in $CHCl_3$) 3419 (OH), 2928 (CH), 1654 (C=O), 1602 (C=O), 1458, 1380 (C=C) cm^{-1}; ^{1}H NMR (400 MHz) δ 0.85 (6H, s, 2 x C*H*$_3$),

1.08-1.39 (4H, m, *Cy*), 1.45-1.54 (2H, m, *Cy*), 1.64-1.78 (2H, m, *Cy*), 1.90-2.05 (6H, m, *Cy*), 2.12-2.19 (2H, m, *Cy*), 2.43 (2H, d, *J* = 12.8, C*H*$_2$Ar), 2.53 (2H, d, *J* = 12.8, C*H*$_2$Ar), 4.60 (2H, s, C=C*H*$_2$), 4.69 (2H, s, C=C*H*$_2$), 6.77 (2H, s, 2 x Ar*H*); ^{13}C NMR (100 MHz) δ 22.7 (2 x *C*H$_2$), 23.2 (2 x *C*H$_3$), 32.0 (2 x Cq), 34.7 (2 x *C*H$_2$), 35.3 (2 x Ar*C*H$_2$), 37.3 (2 x *C*H$_2$), 38.4 (2 x Cq), 47.7 (2 x *C*H$_2$), 108.7 (2 x C=*C*H$_2$), 120.5 (2 x Cq), 130.4 (2 x Ar), 147.3 (2 x Cq), 152.4 (2 x Cq), 182.0 (2 x C=O), 185.5 (2 x C=O); *m/z* (ESI$^-$) 489 (100% M-H$^-$); HRMS: found 489.2301, $C_{30}H_{33}O_6$ requires 489.2283.

1-(1,3-Dimethyl-cyclohexyl)-methyl-10-(1,3-dimethyl-cyclohexyl)-methyl-2,3,9-trihydroxydibenzo[5,6]-furan-8,11-dione (134)

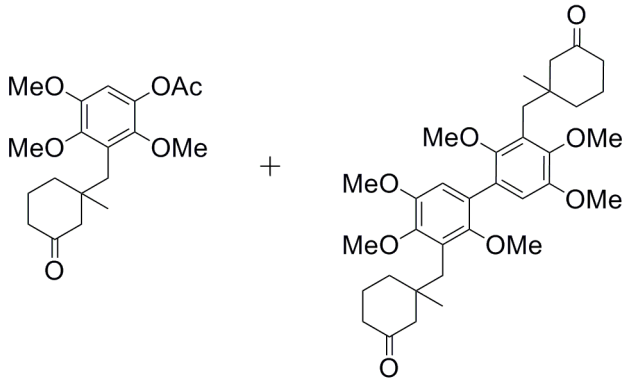


134

To a solution of bis-quinone **133** (13.0 mg, 260 μmol) in benzene (2 mL) under N_2 was added conc. HCl (2 drops) and the solution was stirred and heated to reflux for 48 h. The purple solution was then cooled to rt and diluted with hexanes (5 mL) to give a black precipitate. The suspension was filtered and the filter cake washed with hexanes (2 x 5 mL) to give crude dibenzofuran **134** (3.4 mg, 26%) as a dark purple solid, (which was unstable to purification *via* flash column chromatography) as an inseparable mixture of diastereoisomers; mp. >220 °C; R_f 0.89 (EtOAc/hexanes); IR υ_{max} (solution in $CHCl_3$) 2975 (CH), 2924 (CH), 2873 (CH), 1647 (C=O), 1567, 1513, 1457, 1286, 1218, 1150, 1082 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.70 (m, *Cy*), 0.81 (1.5H, s, C*H*$_3$), 0.82 (1.5H, s, C*H*$_3$), 0.83 (1.5H, s, C*H*$_3$), 0.84 (1.5H, s, C*H*$_3$), 0.85-0.93 (m, *Cy*), 0.95 (3H, s, C*H*$_3$), 0.99 (3H, s, C*H*$_3$), 1.01-1.46 (m, *Cy*), 1.49-1.58 (2H, m, 2 x C*H*), 1.70-1.90 (m, *Cy*), 2.43 (1H, d, *J* = 1.8, ArC*H*$_2$), 2.58 (1H, d, *J* = 1.8, ArC*H*$_2$), 2.84 (1H, d, *J* = 1.8, ArC*H*$_2$), 2.95 (0.5H, d, *J* = 13.3, ArC*H*$_2$), 3.03 (0.5H, d, *J* = 13.4, ArC*H*$_2$), 6.16 (0.5H, d, *J* = 11.5, Ar*H*), 6.20 (0.5H, d, *J* = 6.6, Ar*H*), 7.25 (0.5H, s, O*H*), 7.26 (0.5H, s, O*H*), 7.57 (0.5H, s, O*H*), 7.58 (0.5H, s, O*H*), 7.60 (0.5H,

s, O*H*), 7.61 (0.5H, s, O*H*); ^{13}C NMR (100 MHz) δ 22.2 (2 x *C*H_2), 22.3 (*C*H_2), 22.4 (*C*H_2), 22.6 (*C*H_3), 22.7 (*C*H_3), 23.1 (2 x *C*H_3), 23.2 (2 x *C*H_3), 27.9 (*C*H), 28.0 (*C*H), 28.1 (2 x *C*H), 29.1 (Ar*C*H_2), 29.4 (*C*H_2), 29.7 (2 x *C*H_3), 30.7 (Ar*C*H_2), 32.0 (*C*H_2), 35.1 (2 x *C*H_2), 35.2 (2 x *C*H_2), 36.4 (2 x Cq), 37.3 (2 x Cq), 37.5 (Ar*C*H_2), 37.7 (*C*H_2), 38.6 (Ar*C*H_2), 39.3 (CH_2), 46.7 (*C*H_2), 47.1 (*C*H_2), 47.5 (*C*H_2), 48.0 (*C*H_2), 103.8 (Ar), 103.9 (Ar), 110.9 (C1), 111.6 (C1), 114.7 (C12), 114.8 (C12), 117.6 (2 x C10), 125.4 (2 x C5), 143.6 (C3), 143.8 (C3), 147.4 (2 x C7), 147.6 (2 x C6), 153.3 (C9), 153.5 (C9), 154.3 (2 x C2), 170.5 (C8, C=O), 170.7 (C8, C=O), 185.6 (C11, C=O), 185.7 (C11, C=O); *m/z* (ESI$^-$) 493 (100% M^+-H^-); HRMS found 493.2612 $C_{30}H_{37}O_6$ requires 493.2590.

2,4,5-Trimethoxy-3-((1-methyl-3-oxocyclohexyl)methyl)-phenyl acetate (158) and 3,3'-Bis-[(1-methyl-3-oxocyclohexyl)-methyl]-(2,4,5,2',4',5'-hexamethoxy)-biphenyl (157)[76]

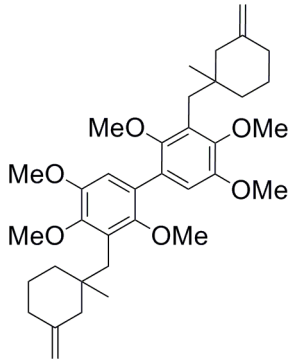


158 **157**

To a degassed solution of $Tl(OAc)_3$ (920 mg, 2.43 mmol, 0.5 equiv.) in CH_3CN (50 mL) under argon was added a degassed solution of ketone **143** (1.42 g, 4.86 mmol) in CH_3CN (25 mL) *via* cannula and the solution cooled to –40 °C before $BF_3.OEt_2$ (2.36 mL, 5.83 mmol, 1.2 equiv.) was added. The bright yellow mixture was warmed to rt and stirred for 1 h after which the now dark green reaction mixture was diluted with CH_2Cl_2 (70 mL) and H_2O (50 mL). The layers were separated and the aq. layer extracted with CH_2Cl_2 (50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/pet. ether) gave in order of elution **158** (187 mg, 11%, lit.[76] 17%) as a light yellow solid; mp. 100-102 °C (lit.[76] mp. 102 °C); R_f 0.60 (40% EtOAc/pet. ether); ^{1}H NMR (500 MHz) δ 0.88 (3H, s, C*H*$_3$), 1.55-1.70 (3H, m, *Cy*), 1.75-1.85 (1H, m, *Cy*), 1.90-2.00 (1H, m, *Cy*), 2.06 (1H, d, *J* = 13.7, *Cy*), 2.15-2.28 (2H, m, *Cy*), 2.31 (3H, s,

C*H*$_3$), 2.60 (1H, d, *J* = 12.9, ArC*H*$_2$), 2.64 (1H, d, *J* = 12.9, ArC*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 6.33 (1H, s, Ar*H*) and **157** (0.70 g, 49%, lit.[76] 45%) as a yellow solid; mp. 123-125 °C (lit.[76] mp. 124-126 °C); R_f 0.50 (40% EtOAc/pet. ether); ^{1}H NMR (400 MHz) δ 0.95 (6H, s, 2 x C*H*$_3$), 1.61-1.68 (2H, m, *Cy*), 1.70-1.79 (2H, m, *Cy*), 1.80-1.90 (2H, m, *Cy*), 1.94-2.03 (2H, m, *Cy*), 2.16 (2H, d, *J* = 13.6, *Cy*), 2.21-2.23 (2H, m, *Cy*), 2.24-2.28 (2H, m, *Cy*), 2.43 (2H, d, *J* = 13.6, *Cy*), 2.70 (4H, s, C*H*$_2$Ar), 3.32 (6H, s, 2 x OC*H*$_3$), 3.85 (12H, s, 4 x OC*H*$_3$), 6.83 (2H, s, Ar*H*). Data in agreement with that reported.[76]

3,3'-Bis-[(1-methyl-3-methylene-cyclohexyl)-methyl]-(2,4,5, 2',4',5'-hexamethoxy)-biphenyl (159)

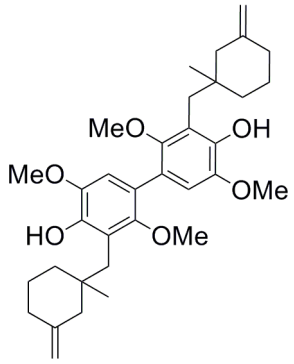


159

To a suspension of methyltriphenylphosphonium bromide (0.95 g, 2.7 mmol, 2.4 equiv.) in Et_2O (100 mL) at 0 °C under N_2 was added *n*-butyllithium (1.1 mL, 2.7 mmol of a 2.5 M sol. in hexanes, 2.4 equiv.) and the mixture was stirred at 0 °C for 1 h. To the mixture was added ketone **157** (0.65 g, 1.1 mmol) in Et_2O (15 mL) and the reaction stirred for a further 30 min before H_2O (35 mL) was added and the layers separated. The aq. layer was extractred with Et_2O (50 mL) and the combined organics washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **159**. Purification by flash column chromatography (10% Et_2O/pet. ether) gave **159** (255 mg, 40%) as a white solid; mp. 88-91 °C; R_f 0.46 (10% Et_2O/pet. ether); IR υ_{max} (solution in $CHCl_3$) 2934 (CH), 1474, 1424, 1392, 1096, 1062, 1013 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.86 (6H, s, 2 x C*H*$_3$), 1.38-1.44 (2H, m, *Cy*), 1.45-1.54 (4H, m, *Cy*), 1.61-1.70 (2H, m, *Cy*), 1.91-2.00 (4H, m, *Cy*), 2.11-2.19 (4H, m, *Cy*), 2.62 (2H, d, *J* = 12.4, ArC*H*$_2$), 2.67 (2H, d, *J* = 12.8, ArC*H*$_2$), 3.35 (6H, s, 2 x OC*H*$_3$), 3.85 (12H, s, 4 x OC*H*$_3$), 4.57 (2H, s, C=C*H*$_2$), 4.66 (2H, s, C=C*H*$_2$), 6.82 (2H, s, Ar*H*);

^{13}C NMR (100 MHz) δ 23.7 (2 x *C*H_2), 24.0 (2 x *C*H_3), 35.1 (2 x *C*H_2), 37.1 (2 x *C*H_2), 37.4 (2 x *C*H_2), 38.3 (2 x Cq), 47.6 (2 x *C*H_2), 56.1 (2 x O*C*H_3), 60.3 (2 x O*C*H_3), 60.4 (2 x O*C*H_3), 108.1 (2 x C=*C*H_2), 112.9 (2 x Ar), 126.8 (2 x Cq), 127.0 (2 x Cq), 148.1 (2 x Cq), 148.5 (2 x Cq), 148.6 (2 x Cq), 151.3 (2 x Cq); *m/z* (ESI$^+$) 601 (100%, MNa^+), 596 (94%, MNH_4^+), 579 (88%, MH^+); HRMS: found 579.3662, $C_{36}H_{51}O_6$ requires 579.3680; Anal. Cald. For $C_{36}H_{50}O_6$: C, 74.71, H, 8.71. Found C, 74.55, H, 8.67%.

3,3'-Bis-[(1-methyl-3-methylenecyclohexyl)-methyl]-(2,5,2'5'-tetramethoxy)-biphenyl-4,4'-diol (160)



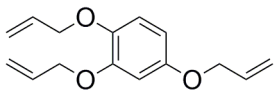
160

To a solution of diphenylphosphine (24 μL, 0.14 mmol, 4.0 equiv.) in THF (10 mL) at 0 °C under N_2 was added *n*-butyllithium (55 μL, 0.14 mmol as a 2.5 M sol. in hexanes, 4.0 equiv.) dropwise. The reaction was stirred at rt for 30 min after which time arene **159** (20 mg, 40 μmol) in THF (3 mL) was added *via* cannula. The reaction mixture was heated at reflux for 18 h before being allowed to cool to rt and H_2O (15 mL) was added. The layers were separated and the aq. layer extracted with Et_2O (15 mL). The combined organics were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **160**. Purification by flash column chromatography (25% EtOAc/pet. ether) gave diol **160** (8.0 mg, 42%) as a colourless oil; R_f 0.72 (25% EtOAc/pet. ether); IR υ_{max} (solution in $CHCl_3$) 3690 (OH), 2931 (CH), 2360, 1601, 1476 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.90 (6H, s, 2 x C*H*$_3$), 1.43-1.55 (6H, m, *Cy*), 1.62-1.71 (2H, m, *Cy*), 1.91-2.03 (4H, m, *Cy*), 2.12-2.21 (4H, m, *Cy*), 2.66 (2H, d, *J* = 12.4, ArC*H*$_2$), 2.70 (2H, d, *J* = 12.8, ArC*H*$_2$), 3.36 (6H, s, 2 x OC*H*$_3$), 3.87 (6H, s, 2 x OC*H*$_3$), 4.55 (2H, s, C=C*H*$_2$), 4.65 (2H, s, C=C*H*$_2$), 5.74 (2H, s, O*H*), 6.80 (2H, s, Ar*H*); *m/z* (ESI$^+$) 573 (47%,

MNa^+), 568 (10%, MNH_4^+), 551 (12%, MH^+); HRMS: found 551.3372, $C_{34}H_{47}O_6$ requires 551.3367.

5.4.2 Protecting Group Studies

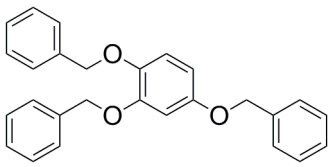
1,2,4-Tris-allyloxy-benzene (164)



164

To a solution of 1,2,4-trihydroxybenzene (1.00 g, 7.94 mmol) in Me_2CO (100 mL) under N_2 was added K_2CO_3 (6.58 g, 47.6 mmol, 6.0 equiv.), followed by TBAI (300 mg, 794 μmol, 0.1 equiv.) and allyl bromide (4.14 mL, 47.6 mmol, 6.0 equiv). The mixture was heated to reflux for 18 h before being allowed to cool to rt and H_2O (100 mL) and Et_2O (100 mL) added. The aq. phase was extracted with Et_2O (2 x 100 mL) and the combined organics washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **164**. Purification by flash column chromatography (20% Et_2O/pet. ether) gave **164** (1.52 g, 77%) as a pale yellow oil; R_f 0.40 (20% Et_2O/pet. ether); IR υ_{max} (solution in $CHCl_3$) 3068 (CH), 3011 (CH), 2923 (CH), 2868 (CH), 1597, 1508 (C=C), 1457, 1423 cm^{-1}; ^1H NMR (400 MHz) δ 4.48 (2H, dt, *J* = 5.3, 1.5, C*H*$_2$OAr), 4.55 (2H, dt, *J* = 5.5, 1.5, C*H*$_2$OAr), 4.59 (2H, dt, *J* = 5.2, 1.6, C*H*$_2$OAr), 5.27 (3H, m, CH=C*H*H), 5.40 (1H, dq, *J* = 7.2, 1.6, CH=C*H*H), 5.43 (1H, dq, *J* = 3.2, 1.6, CH=C*H*H), 5.43 (1H, dq, *J* = 6.8, 1.6, CH=C*H*H), 6.04 (1H, app. dquint, *J* = 10.4, 5.2, C*H*=CH_2), 6.05-6.08 (1H, m, C*H*=CH_2), 6.09 (1H, ddt, *J* = 18.0, 5.2, 4.8, C*H*=CH_2), 6.41 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.56 (1H, d, *J* = 2.8, Ar*H*), 6.83 (1H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (100 MHz) δ 69.4 (*C*H_2), 69.8 (*C*H_2), 71.1 (*C*H_2), 103.1 (Ar), 105.0 (Ar), 115.8 (Ar), 117.4 (*C*H_2), 117.6 (*C*H_2), 117.6 (*C*H_2), 133.3 (*C*H), 133.5 (*C*H), 134.0 (*C*H), 142.9 (Cq), 149.7 (Cq), 153.6 (Cq); *m/z* (ESI^+) 269 (100%, MNa^+), 247 (37%, MH^+); HRMS: found 269.1146, $C_{15}H_{18}O_3Na$ requires 269.1148, found 247.1329, $C_{15}H_{19}O_3$ requires 247.1329; Anal. Cald. For $C_{15}H_{18}O_3$: C, 73.15, H, 7.37. Found C 73.34, H 7.35%.

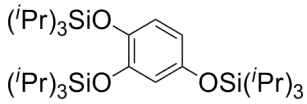
1,2,4-Tris-benzyloxy-benzene (165)[114]



165

To a solution of 1,2,4-trihydroxybenzene (300 mg, 2.38 mmol) in Me_2CO (20 mL) under N_2 was added benzyl bromide (1.41 mL, 11.9 mmol, 5.0 equiv.) followed by K_2CO_3 (3.29 g, 23.8 mmol, 10.0 equiv.). The mixture was heated at reflux for 15 h, before being allowed to cool to rt and concentrated *in vacuo*. The mixture was partitioned between EtOAc (20 mL) and 1 M HCl (20 mL). The aq. layer was washed with EtOAc (20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **165**. Purification by flash column chromatography (20% EtOAc/pet. ether) gave **165** (650 mg, 69%, lit.[114] 88%) as a pale yellow solid; mp. 79-81 °C (lit.[114] mp. 81-82 °C); R_f 0.60 (20% EtOAc/pet. ether); ^{1}H NMR (400 MHz) δ 4.97 (2H, s, C*H*$_2$), 5.09 (2H, s, C*H*$_2$), 5.13 (2H, s, C*H*$_2$), 6.46 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.66 (1H, d, *J* = 2.4, Ar*H*), 6.86 (1H, d, *J* = 8.4, Ar*H*), 7.30-7.50 (15H, m, Ar*H*). Data in agreement with that reported.[114]

1,2,4-Tris-triisopropylsilanyloxy-benzene (166)

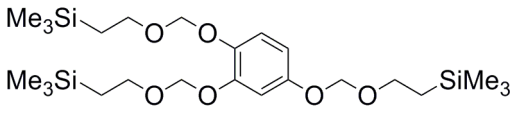


166

To a solution of 1,2,4-trihydroxybenzene (500 mg, 3.97 mmol) in DMF (60 mL) under N_2 was added triisopropylsilyl chloride (7.57 mL, 35.7 mmol, 9.0 equiv.) and the mixture was cooled to 0 °C. To the mixture was added imidazole (6.08 g, 89.3 mmol, 22.5 equiv.) and the mixture was stirred at 0 °C for a further 30 min before being warmed to rt and stirred for 15 h. To the mixture was added Et_2O (70 mL) and H_2O (40 mL) and the layers separated. The aq. layer was extracted with Et_2O (2 x 30 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (40 mL), H_2O (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **166**. Purification by flash column chromatography (10% Et_2O/hexanes) gave arene **166** (1.19 g, 76%) as a colourless oil; R_f 0.81 (10% Et_2O/hexanes); IR υ_{max} (solution in $CHCl_3$) 2947 (CH), 2893 (CH), 2867 (CH), 1506 cm^{-1}; ^{1}H NMR (400 MHz)

δ 1.05-1.14 (54H, m, 18 x C*H*$_3$), 1.16-1.31 (9H, m, 9 x C*H*(CH$_3$)$_2$), 6.32 (1H, dd, *J* = 8.8, 3.0, Ar*H*), 6.43 (1H, d, *J* = 2.8, Ar*H*), 6.66 (1H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (100 MHz) δ 12.7 (*C*H), 12.9 (*C*H), 12.9 (*C*H), 13.1 (*C*H), 13.2 (2 x *C*H), 13.3 (*C*H), 13.5 (2 x *C*H), 17.4 (*C*H$_3$), 17.5 (*C*H$_3$), 17.6 (*C*H$_3$), 17.8 (*C*H$_3$), 17.9 (2 x *C*H$_3$), 18.0 (*C*H$_3$), 18.1 (2 x *C*H$_3$), 111.9 (Ar), 112.3 (Ar), 119.8 (Ar), 141.5 (Cq), 147.0 (Cq), 149.7 (Cq); *m/z* (ESI$^+$) 595 (100%, MH$^+$), 617 (25%, MNa$^+$); HRMS: found 595.4378, $C_{33}H_{67}O_3Si_3$ requires 595.4393, found 617.4197, $C_{33}H_{66}NaO_3Si_3$ requires 617.4212; Anal. Cald. For $C_{33}H_{66}O_3$: C, 66.60, H, 11.18. Found C, 66.88, H, 11.22%.

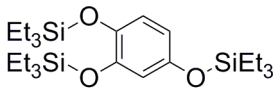
1,2,4-Tris-(2-trimethylsilanyl-ethoxymethoxy)-benzene (167)



167

To a solution of 1,2,4-trihydroxybenzene (150 mg, 1.19 mmol) in CH_2Cl_2 (15 mL) under N_2 at 0 °C was added *i*-Pr$_2$NEt (2.07 mL, 11.9 mmol, 10.0 equiv.) and (trimethylsilyl)ethoxymethyl chloride (1.48 mL, 8.33 mmol, 7.0 equiv.) and the solution was stirred at 0 °C for 30 min. The mixture was then warmed to rt and stirred for a further 16 h before H_2O (15 mL) and Et_2O (15 mL) were added and the layers separated. The aq. phase was extracted with Et_2O (2 x 20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **167**. Purification by flash column chromatography (5% Et_2O/hexanes) gave **167** (201 mg, 33%) as a yellow oil; R_f 0.25 (5% Et_2O/hexanes); IR υ_{max} (thin film) 2953 (CH), 2897, 1507, 1248 (C-O), 1077 cm^{-1}; ^{1}H NMR (300 MHz) δ -0.10-0.15 (27H, m, 3 x Si(C*H*$_3$)$_3$), 0.90-1.00 (6H, m, 3 x C*H*$_2$Si), 3.72-3.84 (6H, m, 3 x C*H*$_2$CH$_2$Si), 5.15 (2H, s, OC*H*$_2$O), 5.19 (2H, s, OC*H*$_2$O), 5.25 (2H, s, OC*H*$_2$O), 6.64 (1H, d, *J* = 8.8, 2.9, Ar*H*), 6.93 (1H, d, *J* = 2.9, Ar*H*), 7.08 (1H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (75 MHz) δ -1.4 (9 x Si(*C*H$_3$)$_3$), 18.1 (3 x *C*H$_2$), 66.0 (*C*H$_2$), 66.2 (*C*H$_2$), 66.3 (*C*H$_2$), 93.5 (*C*H$_2$), 93.9 (*C*H$_2$), 94.6 (*C*H$_2$), 106.4 (Ar), 109.1 (Ar), 117.7 (Ar), 142.3 (Cq), 148.3 (Cq), 152.9 (Cq); *m/z* (ESI$^+$) 539 (100%, MNa$^+$); HRMS: found 539.2674, $C_{24}H_{48}O_6Si_3Na$ requires 539.2656.

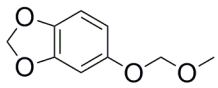
1,2,4-Tris-triethylsilanyloxy-benzene (168)



168

To a solution of 1,2,4-trihydroxybenzene (150 mg, 1.19 mmol) in CH_2Cl_2 (15 mL) under N_2 at 0 °C was added imidazole (567 mg, 8.33 mmol, 7.0 equiv.) and triethylsilyl chloride (1.40 mL, 8.33 mmol, 7.0 equiv.). The solution was stirred at 0 °C for 30 min before being warming to rt and stirred for a further 16 h. To the solution was added H_2O (15 mL) and Et_2O (15 mL) and the layers separated. The aq. layer was extracted with Et_2O (2 x 20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **168**. Purification by flash column chromatography (2% Et_2O/hexanes) gave **168** (540 mg, 97%) as a yellow oil; R_f 0.60 (2% Et_2O/hexanes); IR υ_{max} (thin film) 2956 (CH), 2878 (CH), 1505, 1253, 1175 cm^{-1}; ^1H NMR (300 MHz) δ 0.66-0.81 (18H, m, 3 x (CH_2CH_3)$_3$), 0.95-1.02 (27H, m, 3 x (CH_2CH_3)$_3$), 6.32 (1H, dd, *J* = 8.6, 2.9, Ar*H*), 6.38 (1H, d, *J* = 2.8, Ar*H*), 6.65 (1H, d, *J* = 8.6, Ar*H*); ^{13}C NMR (75 MHz) δ 4.7 (3 x CH_2), 4.9 (3 x CH_2), 5.1 (3 x CH_2), 5.5 (3 x CH_3), 6.6 (3 x CH_3), 6.6 (3 x CH_3), 112.5 (Ar), 112.6 (Ar), 120.4 (Ar), 141.3 (Cq), 146.9 (Cq), 149.6 (Cq); *m/z* (ESI^+) 469 (100%, MH^+); HRMS: found 469.2980, $C_{24}H_{48}O_3Si_3$ requires 469.2990; Anal. Cald. For $C_{24}H_{48}O_3Si_3$: C, 61.48, H, 10.32. Found C, 61.09, H, 10.40%.

5-Methoxymethoxy-benzo[1,3]dioxole (170)[115]

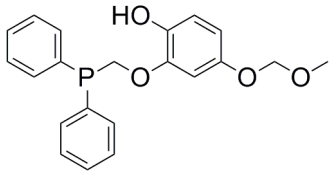


170

To a solution of sesamol **169** (720 mg, 5.21 mmol) in DMF (35 mL) under N_2 was added K_2CO_3 (1.44 g, 10.4 mmol, 2.0 equiv.) and methyl chloromethyl ether (790 μL, 10.4 mmol, 2.0 equiv.) and the mixture was stirred at rt for 5 h. A further portion of K_2CO_3 (720 mg, 5.21 mmol, 1.0 equiv.) and methyl chloromethyl ether (393 μL, 5.21 mmol, 1.0 equiv.) were then added and the reaction stirred for a further 15 h. To the mixture was added H_2O (50 mL) and Et_2O (50 mL) and the layers separated. The aq. layer was extracted with Et_2O (50 mL) and the combined organics washed with 1 M HCl (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to

give crude **170**. Purification by flash column chromatography (10% Et_2O/hexanes) gave **170** (570 mg, 60%, lit.[115] 74%) as a pale yellow oil; R_f 0.33 (10% Et_2O/hexanes); ^1H NMR (400 MHz) δ 3.49 (3H, s, OC*H*$_3$), 5.09 (2H, s, OC*H*$_2$OCH$_3$), 5.92 (2H, s, OC*H*$_2$O), 6.50 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.64 (1H, d, *J* = 2.4, Ar*H*), 6.71 (1H, d, *J* = 8.4, Ar*H*). Data in agreement with that reported.[115]

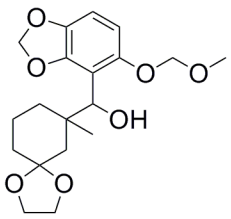
2-[(Diphenylphosphanyl)-methoxy]-4-methoxymethoxyphenol (172)



172

To a solution of diphenylphosphine (416 μL, 2.39 mmol, 5.0 equiv.) in THF (20 mL) at 0 °C under N_2 was added *n*-butyllithium (956 μL, 2.39 mmol of a 2.5 M sol. in hexanes, 5.0 equiv.). The mixture was warmed to rt and stirred for 30 min before MOM-sesamol **170** (87.0 mg, 478 μmol) in THF (5 mL) was added *via* cannula. The mixture was stirred and heated to reflux for 18 h before being cooled to rt. To the mixture was added H_2O (30 mL) and Et_2O (30 mL) and the layers separated. The aq. phase was extracted with Et_2O (3 x 30 mL) and the combined organics washed with H_2O (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **172**. Purification by flash column chromatography (10% Et_2O/hexanes) gave **172** (20 mg, 11%) as a pale yellow oil; R_f 0.12 (10% Et_2O/hexanes); IR υ_{max} (solution in $CHCl_3$) 3684 (OH), 3011 (CH), 2415 (PCH_2) 1506, 1477, 1425, 1334 cm^{-1}; ^1H NMR (400 MHz) δ 3.47 (3H, s, OC*H*$_3$), 4.78 (2H, d, *J* = 6.0, PC*H*$_2$O), 5.10 (2H, s, OC*H*$_2$O), 6.52 (1H, dd, *J* = 7.4, 2.8, Ar*H*), 6.65 (1H, d, *J* = 3.2, Ar*H*), 6.91 (1H, d, *J* = 8.8, Ar*H*), 7.39-7.42 (6H, m, PAr*H*), 7.50-7.54 (4H, m, PAr*H*); ^{13}C NMR (100 MHz) δ 55.9 (O*C*H$_3$), 69.9 (1C, d, *J* = 14.0, P*C*H$_2$), 95.0 (*C*H$_2$OCH$_3$), 104.4 (Ar), 107.3 (Ar), 113.9 (Ar), 128.8 (4C, d, *J* = 6.0, 4 x Ar), 129.3 (2 x Ar), 133.0 (4C, d, *J* = 19.0, 4 x Ar), 146.9 (Cq), 152.7 (Cq), other quaternary carbons could not be distinguished, ^{31}P NMR (162 MHz) δ -16.78 (1P, s); *m/z* (ESI^+) 369 (36%, MH^+), 391 (33%, MNa^+), 759 (100% $2MNa^+$); HRMS: found 369.1253, $C_{21}H_{22}O_4P$ requires 369.1250, found 391.1069, $C_{21}H_{21}O_4PNa$ requires 391.1070.

(5-Methoxymethoxy-benzo[1,3]dioxol-4-yl)-(7-methyl-1,4-dioxa-spiro[4.5]dec-7-yl)-methanol (171)

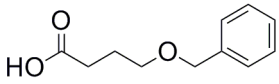


171

To a solution of MOM-sesamol **170** (290 mg, 1.62 mmol, 3.0 equiv.) in THF (7 mL) at 0 °C under N_2 was added *n*-butyllithium (650 μL, 1.62 mmol of a 2.5 M sol. in hexanes, 3.0 equiv.) and the mixture stirred at 0 °C for 1 h. The mixture was then cooled to −78 °C and a solution of aldehyde **139** (100 mg, 540 μmol) in THF (5 mL) was added and the mixture stirred at −78 °C for 30 min before being warmed to rt and stirred for a further 1 h. To the mixture was added H_2O (10 mL) and 1 M HCl (10 mL) and the layers separated. The aq. layer was extracted with Et_2O (2 x 20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **171**. Purification by flash column chromatography (10% Et_2O/hexanes) gave **171** (134 mg, 67%) as a yellow oil, as an inseparable 1:1 mixture of diastereoisomers; R_f 0.10 (10% Et_2O/hexanes); IR υ_{max} (solution in $CHCl_3$) 3582 (OH), 3541 (OH), 3056 (CH), 2953 (CH), 2889 (CH), 1456, 1241 (C-O) cm^{-1}; ^1H NMR (400 MHz) δ 1.03 (1.5H, s, CC*H*$_3$), 1.08 (1.5H, s, CC*H*$_3$), 1.10-1.90 (8H, m, *Cy*), 3.47 (3H, s, CH_2OCH_3), 3.82-3.96 (4H, m, OCH_2CH_2O), 5.11 (2H, s, CH_2OCH_3), 5.91 (2H, s, OCH_2O), 6.60 (1H, d, *J* = 8.4, Ar*H*), 6.64 (1H, d, *J* = 8.4, Ar*H*); ^{13}C NMR (100 MHz) δ 19.0 (CH_3), 19.7 (CH_2), 32.9 (CH_2), 34.9 (CH_2), 40.8 (CH_2), 42.3 (Cq), 42.4 (Cq), 56.3 (OCH_3), 63.4 (CH_2), 64.4 (CH_2), 95.5 (CH_2), 100.9 (CH_2), 106.4 (Ar), 106.4 (Ar), 109.6 (Cq), 142.2 (Cq), 145.7 (Cq), 150.5 (Cq); *m/z* (ESI^+) 367 (2%, MH^+), 389 (54%, MNa^+), 755 (100% $2MNa^+$); HRMS: found 367.1771, $C_{19}H_{27}O_7$ requires 367.1751, found 389.1582, $C_{19}H_{26}O_7Na$ requires 389.1571.

5.4.3 Towards the Synthesis of 6'-Hydroxyarenarol

4-Benzyloxy-butyric acid (174)[116]

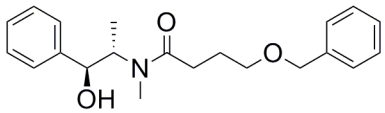


174

Finely ground KOH (23.3 g, 416 mmol, 3.9 equiv.) was added to a mixture of γ-butyrolactone **173** (8.33 mL, 108 mmol) and benzyl bromide (33.3 mL, 281 mmol, 2.6 equiv.) stirred in toluene (133 mL) at rt. The mixture was then heated at reflux for 3 days before being allowed to cool to rt. To the mixture was added Et_2O (100 mL) and H_2O (100 mL) and the layers separated. The aq. phase was extracted with Et_2O (2 x 75 mL) and the combined organics were used as described below. The aq. phase was cooled to 0 °C, acidified with 6 M H_2SO_4 and extracted with Et_2O (3 x 75 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil.

To the initial organic phase from above was added H_2O (70 mL) and KOH (10.0 g) and the mixture was heated at reflux for three days. The resulting solution was diluted with H_2O (100 mL) and extracted with Et_2O (2 x 70 mL). The aq. phase was cooled, acidified as above and extracted with Et_2O (3 x 70 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil. This was combined with that obtained above to give carboxylic acid **174** (17.9 g, 85%, lit.[116] 84%) as a colourless oil; R_f 0.50 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 1.96 (2H, quint, J = 6.7, CH_2CH$_2$OBn), 2.50 (2H, t, J = 7.2, CH_2COOH), 3.55 (2H, t, J = 6.2, CH_2OBn), 4.52 (2H, s, OCH_2Ph), 7.28-7.38 (5H, m, Ar*H*). Data in agreement with that reported.[116]

4-Benzyloxy-*N*-((1*S*, 2*S*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-butyramide (176)[55]

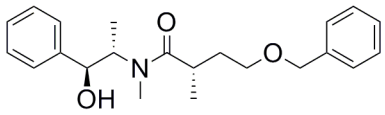


176

To a solution of carboxylic acid **174** (37.3 g, 192 mmol, 1.3 equiv.) in Et_2O (890 mL) under N_2 was added Et_3N (26.9 mL, 192 mmol, 1.3 equiv.) The mixture was stirred at rt for 15 min before being cooled to 0 °C and *t*-BuCOCl (23.7 mL, 192 mmol, 1.3

equiv.) was added. A white precipitate formed immediately and the mixture was warmed to rt and stirred for 1 h. The mixture was then cooled to –78 °C and a solution of (+)-*pseudo*-ephedrine **174** (24.4 g, 148 mmol, 1.0 equiv.) and Et_3N (20.0 mL, 148 mmol, 1.0 equiv.) in THF (350 mL) was added rapidly *via* cannula. The mixture was stirred at –78 °C for 30 min before being warmed to rt and stirred for a further 30 min. Excess anhydride was quenched by addition of H_2O (350 mL) and the layers were separated. The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 150 mL), 1 M HCl (2 x 150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **176**. Purification by flash column chromatography (50% EtOAc/hexanes) gave **176** (45.2 g, 89%, lit.[55] 91%) as a pale yellow oil; R_f 0.30 (80% EtOAc/hexanes); $[\alpha]_D$ +66.2 (*c* 1.08, $CHCl_3$), [lit.[55] $[\alpha_D]$ +75.9 (*c* 1.08, $CHCl_3$)]; ^1H NMR (400 MHz) (1:2.2 rotamer ratio, asterix denotes signals due to minor rotamer) δ 0.97* (3H, d, *J* = 6.8, CHC*H*$_3$), 1.10 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.91-2.06 (2H, m, C*H*$_2$CH$_2$OBn), 2.43 (1H, dt, *J* = 7.2, 6.4, COC*H*$_2$), 2.35-2.65 (1H, m, COC*H*$_2$), 2.83 (3H, s, NC*H*$_3$), 2.91* (3H, s, NC*H*$_3$), 3.52 (2H, dt, *J* = 6.4, 1.2, C*H*$_2$OBn), 3.58* (2H, dt, *J* = 6.4, 1.6, C*H*$_2$OBn), 4.05 (1H, m, C*H*CH$_3$), 4.50 (2H, s, C*H*$_2$Ph), 4.52* (2H, s, C*H*$_2$Ph), 4.45-4.61 (1H, m, C*H*OH), 7.28-7.38 (10H, m, Ar*H*); Anal. Cald. For $C_{21}H_{27}NO_3$: C, 73.87, H, 7.97, N, 4.10. Found C, 73.57, H, 8.15, N, 4.22%. Data in agreement with that reported.[55]

(*S*)-4-Benzyloxy-*N*-((1*S*,2*S*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-2-methyl-butyramide (177)[55]

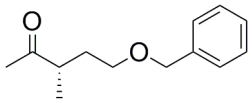


177

LiCl (15.5 g, 366 mmol, 7.0 equiv.) was flame dried under vacuum and cooled under N_2. To this was added THF (60 mL) and *i*-Pr_2NH (16.6 mL, 120 mmol, 2.3 equiv.) and the suspension was cooled to -78 °C. To the suspension was added *n*-butyllithium (57.2 mL, 110 mmol of a 1.9 M sol. in hexanes, 2.1 equiv.) over 15 min. The mixture was then warmed to 0 °C for 5 min, re-cooled to –78 °C and *pseudo*-ephedrine amide **176** (17.9 g, 52.3 mmol) in THF (150 mL) was added over 30 min. The mixture was stirred at –78 °C for 1 h, 0 °C for 15 min and rt for 5 min, before being re-cooled to 0 °C and MeI (9.78 mL, 157 mmol, 3.0 equiv.) added. The

mixture was stirred at 0 °C for 15 min before sat. aq. NH_4Cl (100 mL) was added followed by EtOAc (100 mL). The layers were separated and the aq. layer extracted with EtOAc (2 x 80 mL). The combined organics were washed with 1 M HCl (2 x 80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **177**. Purification by flash column chromatography (Et_2O) gave **177** (17.1 g, 92%, lit.[55] 96%) as a colourless oil; R_f 0.22 (Et_2O); $[\alpha]_D$ +89.4 (*c* 1.80, $CHCl_3$), [lit.[55] $[\alpha_D]$ +93.6 (*c* 1.88, $CHCl_3$)]; ^{1}H NMR (400 MHz) (1:3.1 rotamer ratio, asterix denotes signals due to minor rotamer) δ 0.97* (3H, d, *J* = 6.6, NCHC*H*$_3$), 1.04 (3H, d, *J* = 6.6, NCHC*H*$_3$), 1.13 (3H, d, *J* = 6.6, COCHC*H*$_3$), 1.16* (3H, d, *J* = 6.6, COCHC*H*$_3$), 1.65-1.71 (1H, m, C*H*$_2$CH$_2$OBn), 1.98-2.04 (1H, m, C*H*$_2$CH$_2$OBn), 2.82 (3H, s, NC*H*$_3$), 2.93* (3H, s, NC*H*$_3$), 2.88-2.95 (1H, m, COC*H*CH$_3$), 3.40-3.45 (1H, m, C*H*$_2$OBn), 3.48-3.53 (1H, m, C*H*$_2$OBn), 4.25-4.45 (1H, m, NC*H*CH$_3$), 4.46 (2H, s, OC*H*$_2$Ph), 4.53-4.63 (1H, m, C*H*OH), 7.25-7.36 (10H, m, Ar*H*). Data in agreement with that reported.[55]

(3*S*)-5-Benzyloxy-3-methyl-pentan-2-one (135)[55]

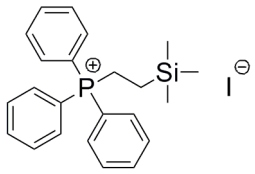


135

To a solution of *pseudo*-ephedrine amide **177** (4.88 g, 13.8 mmol) in THF (120 mL) at –78 °C under N_2 was added methyllithium (20.7 mL, 33.0 mmol, of a 1.6 M sol. in Et_2O, 2.4 equiv.). The mixture was warmed to 0 °C for 15 min before *i*-Pr_2NH (1.93 mL, 13.8 mmol, 1.0 equiv.) was added and the mixture stirred for a further 15 min. A solution of acetic acid/Et_2O (20% v/v, 37 mL) was added and the mixture warmed to rt before Et_2O (40 mL) and H_2O (40 mL) were added and the layers separated. The aq. layer was extracted with Et_2O (2 x 15 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (4 x 15 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **135**. Purification by flash column chromatography (20% EtOAc/hexanes) gave **135** (2.00 g, 71% lit.[55] 81%) as a colourless oil; R_f 0.31 (20 % EtOAc/hexanes); $[\alpha_D]$ +3.6 (*c* 0.98 $CHCl_3$), [lit.[55] $[\alpha_D]$ +10.7 (*c* 0.98, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ 1.11 (3H, d, *J* = 7.2, CHC*H*$_3$), 1.63 (1H, dq, *J* = 14.2, 6.4, C*H*$_2$CH$_2$OBn), 1.98-2.08 (1H, m, C*H*$_2$CH$_2$OBn), 2.14 (3H, s,

COC*H*$_3$), 2.74 (1H, sext, *J* = 6.8, C*H*CH$_3$), 3.48 (2H, t, *J* = 6.0, C*H*$_2$OBn), 4.48 (2H, s, C*H*$_2$Ph), 7.29-7.37 (5H, m, Ar*H*). Data in agreement with that reported.[55]

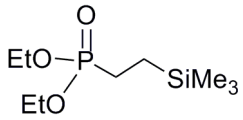
(Trimethylsilylethyl)-triphenylphosphoniumiodide (179)[96]



179

To a solution of methyltriphenylphosphonium bromide (4.40 g, 12.4 mmol) under N_2 in CH_2Cl_2 (100 mL) at 0 °C was added *n*-butyllithium (5.97 mL of a 2.5 M sol. in hexanes, 14.9 mmol, 1.2 equiv.) and the mixture was stirred for 30 min before being warmed to rt and stirred for 1 h. The mixture was then re-cooled to 0 °C and iodo-(methyl)-trimethylsilane (2.50 mL, 14.9 mmol, 1.2 equiv.) was added dropwise before being warmed to rt and stirred for a further 1 h. To the mixture was added H_2O (50 mL) and Et_2O (50 mL) and the layers separated. The aq. layer was extracted with Et_2O (4 x 50 mL) and the combined organics washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **179**. Purification by recrystallisation (H_2O) gave **179** (3.41 g, 76%, lit.[96] 88%) as a white solid; mp. 162-164 °C (lit.[96] mp. 163-165 °C); ^{1}H NMR (400 MHz) δ 0.13 (9H, s, Si(C*H*$_3$)$_3$), 0.68-0.75 (2H, m, C*H*$_2$Si), 3.38-3.45 (2H, m, PC*H*$_2$), 7.69-7.84 (15H, Ar*H*); ^{13}C NMR (100 MHz) δ -1.6 (3 x *C*H$_3$), 8.4 (1C, d, *J* = 8.1, *C*H$_2$Si), 19.1 (1C, d, *J* = 46.2, *C*H$_2$P), 118.0 (3C, d, *J* = 85.2, 3 x Cq), 130.6 (6C, d, *J* = 12.4, 6 x Ar), 134.6 (6C, d, *J* = 9.5, 6 x Ar), 135.2 (3C, d, *J* = 3.0, 3 x Ar), one quaternary carbon could not be distinguished; ^{31}P NMR (162 MHz) δ 26.40 (1P, s); *m/z* (ESI$^+$) 363 (100%, MH$^+$); HRMS: found 363.1717, $C_{23}H_{28}PSi$ requires 363.1692. Data in agreement with that reported.[96]

(2-Trimethylsilanyl-ethyl)-phosphonic acid diethyl ester (180)

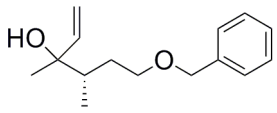


180

To a solution of diethoxymethyl phosphonate (500 mg, 3.27 mmol, 3.0 equiv.) in THF (15 mL) under N_2 at -78 °C was added *n*-butyllithium (2.04 mL of a 2.5 M sol.

in hexanes, 3.27 mmol, 3.0 equiv.). The mixture was warmed to rt and stirred for 30 min before being re-cooled to -78 °C and (iodomethyl)-trimethylsilane (230 mL, 1.09 mmol) added. The mixture was then stirred at -78 °C for 1 h before being warmed to rt and stirred for a further 1 h. Sat. aq. NH_4Cl (50 mL) was added and the layers separated. The aq. layer was extracted with EtOAc (3 x 50 mL) and the combined organics washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **180**. Purification by flash column chromatography (50% EtOAc/hexanes) gave phosphonate **180** (350 mg, 95%) as a colourless oil; R_f 0.11 (50% EtOAc/hexanes); IR υ_{max} (thin film) 2981 (CH), 2952 (CH), 2906 (CH), 1232 (P=O), 1161, 1054, 1023 (P-O) cm^{-1}; ^1H NMR (500 MHz) δ -0.03 (9H, s, Si(CH_3)$_3$), 0.68-0.73 (2H, m, CH_2Si), 1.28 (6H, t, J = 7.1, 2 x CH_2CH_3), 1.56-1.63 (2H, m, PCH_2), 4.01-4.09 (4H, m, 2 x CH_2CH_3); ^{13}C NMR (125 MHz) δ -2.2 (3 x SiCH_3), 8.0 (CH_2Si), 16.5 (2 x CH_3), 19.8 (1C, d, J = 139.9, CH_2P), 61.5 (2 x CH_2); ^{31}P NMR (121 MHz) δ 35.5 (1P, s); *m/z* (FAB$^+$) 239 (7%, MH$^+$), 261 (100% MNa$^+$); HRMS: found 261.1057, $C_9H_{23}O_3PSiNa$ requires 261.1055.

(4*S*)-6-Benzyloxy-3,4-dimethyl-hex-1-en-3-ol (182)[55]

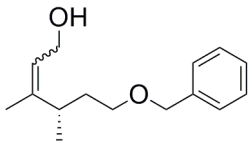


182

To a solution of methyl ketone **135** (11.1 g, 53.6 mmol) in toluene (300 mL) at -78 °C under N_2 was added vinylmagnesium bromide (69.7 mL of a 1 M sol. in THF, 69.7 mmol, 1.3 equiv.) and the mixture was stirred for 10 min before being warmed to rt and stirred for a further 5 h. Sat. aq. NH_4Cl (150 mL) was added and the mixture extracted with Et_2O (3 x 100 mL). The combined organics were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **182**. Purification by rapid filtration through silica and eluting with (10% EtOAc/hexanes) gave **182** (11.0 g, 88%, lit.[55] 58%) as a pale yellow oil, as an inseparable 1:1 mixture of diastereoisomers; R_f 0.13 (10% EtOAc/hexanes); [α_D] -6.4 (*c* 0.39, $CHCl_3$), [lit.[55] [α_D] -10.3 (*c* 0.39, $CHCl_3$)]; ^1H NMR (400 MHz) δ 0.94 (3H, d, J = 7.2, CHCH_3), 1.24 (1.5H, s, CCH_3), 1.27 (1.5H, s, CCH_3), 1.35-1.45 (1H, m, CH_2CH_2OBn), 1.67-1.77 (1H, m, CHCH$_3$), 1.88-1.98 (1H, m, CH_2CH_2OBn), 3.46-3.54 (1H, m, CH_2OBn), 3.55-3.63 (1H, m, CH_2OBn), 4.47-4.57 (2H, m, CH_2Ph), 5.09 (0.5H, dd, J = 10.4, 1.2,

CH=C*H*$_{cis}$), 5.10 (0.5H, dd, *J* = 10.8, 1.6, CH=C*H*$_{cis}$), 5.23 (0.5H, dd, *J* = 17.2, 1.6, CH=C*H*$_{trans}$), 5.24 (0.5H, dd, *J* = 17.6, 1.6, CH=C*H*$_{trans}$), 5.91 (0.5H, dd, *J* = 17.2, 2.4, C*H*=CH$_2$), 5.94 (0.5H, dd, *J* = 17.2, 2.4, C*H*=CH$_2$), 7.25-7.40 (5H, m, Ar*H*). Data in agreement with that reported.[55]

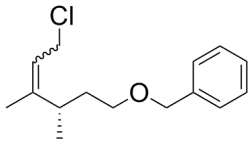
(4*S*)-(*E*,*Z*)-6-Benzyloxy-3,4-dimethyl-hex-2-en-1-ol (183)[55]



183

To a solution of allylic alcohol **182** (1.50 g, 6.41 mmol) in Et$_2$O (45 mL) under N$_2$ at 0 °C was added Ph$_3$SiOReO$_3$ (162 mg, 313 μmol, 5 mol%) in one portion. After 10 min BSA (1.89 mL, 7.69 mmol, 1.2 equiv.) was added and the mixture stirred at 0 °C for a further 15 min before being warmed to rt for 15 h. To the mixture was added Et$_3$N (622 μL) and the mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (66.0 mL) and K$_2$CO$_3$ (1.76 g, 12.6 mmol, 2.0 equiv.) was added. The mixture was stirred at rt for 3 h before sat. aq. NH$_4$Cl (20 mL) was added and the layers separated. The aq. layer was extracted with CH$_2$Cl$_2$ (4 x 15 mL) and the combined organics washed with brine (20 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give crude **183**. Purification by flash column chromatography (20% Et$_2$O/hexanes) gave allylic alcohol **183** (1.00 g, 66%, lit.[55] 6% from **135**) as a colourless oil, (*E*/*Z* 80:20); R$_f$ 0.28 (40% Et$_2$O/hexanes); [α_D] = +9.4 (c 0.38, CHCl$_3$), [lit.[55] [α_D] +15.8 (*c* 0.37, CHCl$_3$)]; ^{1}H NMR (400 MHz) (only signals due to major isomer quoted) δ 1.03 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.60 (3H, s, CC*H*$_3$), 1.55-1.75 (2H, m, C*H*$_2$CH$_2$OBn), 2.34 (1H, sext, *J* = 6.8, C*H*CH$_3$), 3.42 (2H, t, *J* = 6.8, C*H*$_2$OBn), 4.13 (2H, d, *J* = 6.8, C*H*$_2$OH), 4.47 (1H, d, *J* = 12.0, C*H*$_2$Ph), 4.50 (1H, d, *J* = 12.0, C*H*$_2$Ph), 5.42 (1H, td, *J* = 6.0, 0.8, C*H*CH$_2$OH), 7.25-7.40 (5H, m, Ar*H*); Data in agreement with that reported.[55]

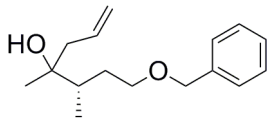
(3*S*)-(*E*,*Z*)-(6-Chloro-3,4-dimethyl-hex-4-enyloxymethyl)-benzene (184)[55]



184

To a stirred solution of *N*-chlorosuccinimide (1.34 g, 10.0 mmol, 1.1 equiv.) in CH_2Cl_2 (45 mL) under N_2 at 0 °C was added dimethyl sulfide (800 μL, 10.9 mmol, 1.2 equiv.) dropwise. The resulting white suspension was cooled to -20 °C and allylic alcohol **182** (2.13 g, 9.12 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 10 min. The reaction mixture was warmed to 0 °C and stirred for 1 h before being poured onto ice cold brine (40 mL) and the layers separated. The aq. layer was extracted with CH_2Cl_2 (2 x 40 mL) and the combined organics washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude allylic chloride **184** (1.78 g, 78%) as a yellow oil, (*E*/*Z* 84:16) which was used without further purification; R_f 0.75 (10% EtOAc/hexanes); [α_D] +3.7 (*c* 0.49 $CHCl_3$), [lit.[55] [α_D] +7.3 (*c* 0.44, $CHCl_3$)]; ^{1}H NMR (400 MHz) (only signals due to major isomer quoted) δ 1.03 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.59-1.74 (2H, m, C*H*$_2$CH$_2$OBn), 1.66 (3H, s, CC*H*$_3$), 2.38 (1H, sext, *J* = 7.4, C*H*CH$_3$), 3.36-3.46 (2H, m, C*H*$_2$OBn), 4.09 (2H, d, *J* = 8.0, C*H*$_2$Cl), 4.49 (2H, s, C*H*$_2$Ph), 5.48 (1H, tq, *J* = 8.0, 0.8, C*H*CH$_2$Cl), 7.25-7.40 (5H, m, Ar*H*). Data in agreement with that reported.[55]

(*S*)-7-Benzyloxy-4,5-dimethyl-hept-1-en-4-ol (217)

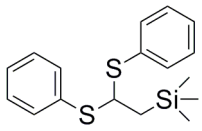


217

To a solution of ketone **135** (0.10 g, 0.49 mmol) in THF (5 mL) under N_2 at 0 °C was added allylmagnesium bromide (0.98 mL, 0.98 mmol of a 1 M sol. in hexanes, 2.0 equiv.) dropwise over 10 min. After the addition the mixture was warmed to rt over 15 h before sat. aq. NH_4Cl (20 mL) was added and the layers separated. The aq. layer was extracted with Et_2O (2 x 15 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **217**. Purification by flash column chromatography (20% EtOAc/hexanes) gave **217** (95 mg, 79%) as a colourless oil, as an inseparable 1:1 mixture of diastereoisomers; R_f 0.43 (20% EtOAc/hexanes); [α_D] –11.9 (*c* 0.77, $CHCl_3$); IR υ_{max} (thin film) 3444 (OH), 2975 (CH), 2942 (CH), 2877 (CH), 1639, 1454, 1365, 1092 (C-O), 1076, 1027 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (1.5H, d, *J* = 6.9, CHC*H*$_3$), 0.95 (1.5H, d, *J* = 6.9, CHC*H*$_3$), 1.09 (1.5H, s, CC*H*$_3$), 1.13 (1.5H, s, CC*H*$_3$), 1.36-1.45 (1H, m, C*H*$_2$CH$_2$OBn), 1.64-1.74 (1H, m, C*H*CH$_3$), 1.89-1.96 (0.5H, m, C*H*$_2$CH$_2$OBn), 1.99-

2.08 (0.5H, m, CH_2CH$_2$OBn), 2.10 (1H, br s, O*H*), 2.20-2.31 (2H, m, CH_2CH), 3.47-3.53 (1H, m, CH_2OBn), 3.56-3.62 (1H, m, CH_2OBn), 4.49-4.57 (2H, m, CH_2Ph), 5.10-5.18 (2H, m, CH=CH_2), 5.76-5.95 (1H, m, C*H*=CH$_2$), 7.28-7.35 (5H, m, Ar*H*); ^{13}C NMR (125 MHz) δ 14.2 (*C*H$_3$), 15.3 (*C*H$_3$), 22.8 (*C*H$_3$), 24.3 (*C*H$_3$), 31.3 (*C*H$_2$), 31.7 (*C*H$_2$), 39.6 (*C*H), 39.7 (*C*H), 43.7 (*C*H$_2$), 45.0 (*C*H$_2$), 69.1 (*C*H$_2$), 69.3 (*C*H$_2$), 73.0 (*C*H$_2$), 73.1 (*C*H$_2$), 74.0 (2 x Cq), 118.5 (*C*H$_2$), 118.6 (*C*H$_2$), 127.7 (Ar), 127.7 (Ar), 127.7 (Ar), 128.3 (Ar), 128.5 (Ar), 134.3 (*C*H), 134.3 (*C*H), 138.4 (2 x Cq); *m/z* (CI$^+$) 249 (7%, MH$^+$), 231 (30%, MH$^+$-H$_2$O), 207 (43%, M-CH$_2$=CHCH$_2$); HRMS: found 249.1856, C$_{16}$H$_{24}$O$_2$ requires 249.1855.

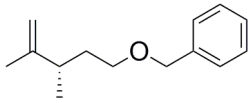
(2,2-Bis-phenylsulfanyl-ethyl)-trimethyl-silane (185)



185

To a solution of bis(phenyl)thiomethane (1.00 g, 4.30 mmol) in THF (10 mL) under N$_2$ at 0 °C was added *n*-butyl lithium (1.98 mL of a 2.5 M sol. in hexanes, 4.95 mmol, 1.2 equiv.) dropwise and the solution stirred at 0 °C for 15 min. To the solution was added (iodomethyl)-trimethylsilane (740 μL, 4.95 mmol, 1.2 equiv.) and the solution warmed to rt and stirred for 3.5 h before H$_2$O (20 mL) and Et$_2$O (20 mL) were added and the layers separated. The aq. phase was extracted with Et$_2$O (3 x 20 mL) and the combined organics washed with H$_2$O (30 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give crude **185**. Purification by flash column chromatography (hexanes) gave **185** (0.68 g, 50%) as a yellow oil; R$_f$ 0.11 (hexanes); IR υ$_{max}$ (thin film) 3047 (CH), 3059 (CH), 2952 (CH), 2895 (CH), 1583, 1490, 1438, 1247 (Si-C) cm^{-1}; ^{1}H NMR (500 MHz) δ 0.09 (9H, s, Si(C*H*$_3$)$_3$), 1.32 (2H, d, *J* = 8.0, CH_2Si), 4.58 (1H, t, *J* = 7.6, C*H*CH$_2$Si), 7.27-7.35 (6H, m, Ar*H*), 7.45-7.49 (4H, m, Ar*H*); ^{13}C NMR (125 MHz) δ -1.2 (Si(*C*H$_3$)$_3$), -1.0 (Si(*C*H$_3$)$_3$), -0.8 (Si(*C*H$_3$)$_3$), 25.1 (*C*H$_2$), 55.1 (*C*H), 127.3 (4 x Ar), 128.8 (4 x Ar), 132.3 (2 x Ar), 134.3 (2 x Cq); *m/z* (FAB$^+$) 341 (25%, MNa$^+$), 209 (100% M$^+$-PhS); HRMS: found 341.0828, C$_{17}$H$_{22}$S$_2$SiNa requires 341.0830.

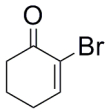
((*S*)-3,4-Dimethyl-pent-4-enyloxymethyl)-benzene (187)



187

To a solution of methyltriphenylphosphonium bromide (3.46 g, 9.70 mmol, 20.0 equiv.) in Et_2O (120 mL) under N_2 at 0 °C was added *n*-butyllithium (3.88 mL, 9.70 mmol of a 2.5 M sol. in hexanes, 20.0 equiv.). The suspension was stirred at 0 °C for 1 h before ketone **135** (100 mg, 485 μmol) in Et_2O (20 mL) was added *via* cannula. The mixture was stirred at 0 °C for a further 30 min before being warmed to rt and stirred for a further 2 h. To the mixture was added H_2O (100 mL) and Et_2O (100 mL) and the layers separated. The aq. layer was extracted with Et_2O (3 x 50 mL) and the combined organics washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **187**. Purification by flash column chromatography (10% Et_2O/hexanes) gave alkene **187** (74.0 mg, 74%) as a colourless oil; R_f 0.66 (10% Et_2O/hexanes); $[\alpha_D]$ +2.3 (*c* 1.00, $CHCl_3$); IR υ_{max} (thin film) 3070 (C-H), 2962 (CH), 2932 (CH), 2857 (CH), 1645, 1454, 1436, 1363, 1202, 1099 cm^{-1}; ^1H NMR (300 MHz) δ 1.05 (3H, d, *J* = 6.9, CHC*H*$_3$), 1.58-1.70 (1H, m, C*H*$_2$CH$_2$OBn), 1.69 (3H, s, CC*H*$_3$), 1.70-1.81 (1H, m, C*H*$_2$CH$_2$OBn), 2.38 (1H, sex, *J* = 7.0, C*H*CH$_3$), 3.49 (2H, t, *J* = 6.7, C*H*$_2$OBn), 4.51 (2H, s, C*H*$_2$Ph), 4.78 (2H, s, C=C*H*$_2$), 7.28-7.38 (5H, m, Ar*H*); ^{13}C NMR (75 MHz) δ 18.9 (*C*H$_3$), 19.8 (*C*H$_3$), 34.8 (*C*H$_2$), 37.9 (*C*H), 68.8 (*C*H$_2$), 73.0 (*C*H$_2$), 109.7 (C=*C*H$_2$), 127.5 (2 x Ar), 127.7 (2 x Ar), 128.4 (Ar), 138.7 (Cq), 149.6 (Cq); *m/z* (FAB$^+$) 205 (30%, MH$^+$), 176 (100%, MH$^+$-29); HRMS: found 205.1590, $C_{14}H_{20}O$ requires 205.1592.

2-Bromo-cyclohex-2-enone (190)[52]

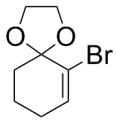


190

To a solution of cyclohexenone **189** (6.75 g, 72.2 mmol) in CH_2Cl_2 (150 mL) at 0 °C under N_2 was added bromine (3.58 mL, 72.2 mmol, 1.0 equiv.) dropwise to give a yellow solution. The solution was stirred at 0 °C for a further 10 min before Et_3N (14.5 mL, 108 mmol, 1.5 equiv.) was added dropwise to give a brown solution. The solution was warmed to rt and stirred for a further 1.5 h before H_2O (100 mL) was

added and the layers separated. The organic layer was washed with 1 M HCl (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **190**. Purification by recrystallisation (hexanes) gave **190** (7.80 g, 62%, lit.[52] 63%) as a white solid; mp. 74-76 °C, (lit.[52] mp. 75-76 °C); R_f 0.24 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 2.06-2.12 (2H, m, C*H*$_2$), 2.46 (2H, app. q, *J* = 6.0, CHC*H*$_2$), 2.65 (2H, app. t, *J* = 6.8, C*H*$_2$CO), 7.44 (1H, t, *J* = 4.6, C=C*H*). Data in agreement with that reported.[52]

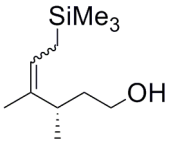
6-Bromo-1,4-dioxa-spiro[4.5]dec-6-ene (84)[52]



84

To a solution of bromoenone **190** (7.80 g, 44.6 mmol) in benzene (250 mL) was added 1,2-dihydroxyethane (9.86 mL, 178 mmol, 4.0 equiv.) and CSA (500 mg, 2.23 mmol, 0.05 equiv.) and the mixture was heated at reflux in Dean Stark apparatus for 15 h. The reaction was cooled, poured onto sat. aq. NH_4Cl (150 mL) and the layers separated. The aq. phase was extracted with EtOAc (2 x 100 mL) and the combined organics washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **84**. Purification by flash column chromatography (5% EtOAc/hexanes) gave acetal **84** (7.56 g, 77%, lit.[52] 91%) as a pale yellow oil; R_f 0.20 (5% Et_2O/hexanes); ^{1}H NMR (400 MHz) δ 1.74-1.81 (2H, m, C*H*$_2$), 1.87-1.93 (2H, m, C*H*$_2$CH), 2.05-2.11 (2H, m, C*H*$_2$CO), 3.93-4.01 (2H, m, OC*H*$_2$C*H*$_2$O), 4.13-4.22 (2H, m, OC*H*$_2$C*H*$_2$O), 6.34 (1H, t, *J* = 4.2, C=C*H*). Data in agreement with that reported.[52]

(3*S*)-(*E*,*Z*)-3,4-Dimethyl-6-trimethylsilyl-hex-4-en-1-ol (178)[55]

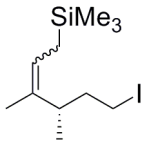


178

To a solution of hexamethyldisilane (7.65 mL, 37.7 mmol, 9.5 equiv.) in HMPA (30.6 mL) at 0 °C under N_2 was added methyllithium (19.9 mL of a 1.5 M sol. in Et_2O as a complex with LiBr, 29.9 mmol, 7.5 equiv.). The reaction mixture was stirred at 0 °C for 15 min before THF (140 mL) was added rapidly and the solution

immediately cooled to -78 °C. To the mixture was added allylic chloride **184** (1.00 g, 4.00 mmol) in THF (20 mL) dropwise *via* cannula over 30 min. The reaction was allowed to warm to rt over 15 h before being poured onto pet. ether (150 mL) and sat. aq. NH_4Cl (150 mL). The layers were separated and the organics washed with H_2O (4 x 40 mL), brine (40 mL), filtered through a silica plug and concentrated *in vacuo* to give crude **178**. Purification by flash column chromatography (10% Et_2O/hexanes) gave **178** (*E*/*Z* 69:31), (470 mg, 59%, lit.[55] 96%) as a colourless oil; R_f 0.33 (10% EtOAc/hexanes); [α_D] +5.6 (*c* 1.07, $CHCl_3$), [lit.[55] [α_D] +8.3 (*c* 1.26, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ -0.09 (9H, s, Si(C*H*$_3$)$_3$), 0.90 (3H, d, *J* = 6.9, CHC*H*$_3$), 1.30 (2H, dd, *J* = 8.6, 0.6, C*H*$_2$Si), 1.38 (3H, s, CC*H*$_3$), 1.40-1.59 (2H, m, C*H*$_2$CH$_2$OH), 2.07 (1H, br s, O*H*), 2.10-2.21 (1H, m, C*H*CH$_3$), 3.46 (2H, dt, *J* = 6.8, 1.2, C*H*$_2$OH), 5.16 (1H, tdq, *J* = 8.5, 1.3, 0.7, C*H*CH$_2$Si). Data in agreement with that reported.[55]

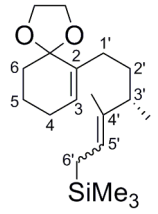
(4*S*)-(*E*,*Z*)-(6-Iodo-3,4-dimethyl-hex-2-enyl)-trimethylsilane (83)[55]



83

To a solution of alcohol **178** (2.00 g, 10.0 mmol) in MeCN (170 mL) at 0 °C under N_2 was added imidazole (885 mg, 13.0 mmol, 1.3 equiv.) and PPh_3 (3.38 g, 13.0 mmol, 1.3 equiv.). To the mixture was added iodine (3.05 g, 12.0 mmol, 1.2 equiv.) in small portions over 30 min and the reaction stirred at rt for 3 h before being poured onto 0.5 M HCl (100 mL) and the layers separated. The aq. layer was extracted with Et_2O (2 x 100 mL) and the combined organics washed with brine (70 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **83**. Purification by flash column chromatography (hexanes) gave iodide **83** (*E*/*Z* 80:20), (2.37 g, 76%, lit.[55] 87%) as a colourless oil; R_f 0.78 (2% EtOAc/hexanes); [α_D] +12.0 (*c* 0.60, $CHCl_3$), [lit.[55] [α_D] +22.6 (*c* 0.50, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ 0.01 (9H, s, Si(C*H*$_3$)$_3$), 1.01 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.35-1.45 (2H, m, C*H*$_2$Si), 1.46 (3H, s, CC*H*$_3$), 1.72-1.95 (2H, m, C*H*$_2$CH$_2$I), 2.24-2.33 (1H, m, C*H*CH$_3$), 2.97-3.22 (2H, m, C*H*$_2$I), 5.28 (1H, t, *J* = 8.8, C*H*CH$_2$Si). Data in agreement with that reported.[55]

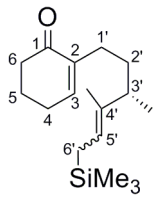
[(3'*S*)-1'-(1,4-Dioxaspiro[4.5]dec-2-enyl)-3',4'-dimethyl-hex-5'-enyl]-trimethylsilane (191)[55]



191

To a solution of vinyl bromide **84** (1.37 g, 6.25 mmol, 2.2 equiv.), in THF (28 mL) under N_2 at -78 °C was added *s*-butyllithium (12.2 mL of a 1.1 M solution in cyclohexane, 12.5 mmol, 4.4 equiv.) dropwise and the reaction stirred for 5 min. To the mixture was added HMPA (2.80 mL) rapidly and the reaction stirred for a further 20 min. A solution of iodide **83** (880 mg, 2.84 mmol) in THF (7 mL) was then added dropwise *via* cannula over 10 min. The reaction was allowed to stir and warm to rt for 15 h after which time H_2O (50 mL) was added and the layers separated. The aq. layer was extracted with Et_2O (3 x 50 mL) and the combined organics washed with H_2O (4 x 40 mL), brine (40 mL), dried ($MgSO_4$), filtered through a silica plug and concentrated *in vacuo* to give crude **191**. Purification by flash column chromatography (10% Et_2O/hexanes) gave coupled ketal **191** (*E*/*Z* 77:23), (630 mg, 68%) as a colourless oil; R_f (0.39 10% Et_2O/hexanes); $[\alpha]_D$ –8.0 (*c* 1.18, $CHCl_3$), no lit. $[\alpha]_D$ reported; ^{1}H NMR (400 MHz) δ -0.01 (9H, s, Si(C*H*$_3$)$_3$), 0.98 (3H, d, *J* = 7.2, CHC*H*$_3$), 1.30-1.55 (4H, m, C2'*H*$_2$ + C6'*H*$_2$), 1.46 (3H, s, CC*H*$_3$), 1.68-1.74 (4H, m, C5*H*$_2$ + C1'*H*$_2$), 1.87-1.95 (2H, m, C6*H*$_2$), 2.02-2.03 (2H, m, C4*H*$_2$), 2.06-2.13 (1H, m, C*H*CH$_3$), 3.97-3.98 (4H, m, OC*H*$_2$C*H*$_2$O), 5.19 (1H, t, *J* = 8.2, C*H*CH$_2$Si), 5.68-5.70 (1H, m, C3*H*). Data in agreement with that reported.[55]

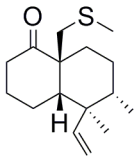
2-[(3'*S*)(*E*,*Z*)-3'4'-Dimethyl-6'-trimethylsilyl-hex-4'enyl]-cyclohex-2-en-1-one (85)[55]



85

To ketal **191** (360 mg, 1.12 mmol) was added THF (5 mL) and 1 M HCl (5 mL) and the reaction stirred vigorously at rt for 5 h until TLC analysis showed complete consumption of starting material. The layers were separated and the aq. extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **85**. Purification by flash column chromatography (10% Et_2O/hexanes) gave ketone **85** (*E*/*Z* 87:13), (268 mg, 86%, lit.[55] 79% from **83**) as a colourless oil; R_f 0.50 (10% Et_2O); $[\alpha_D]$ –15.7 (*c* 1.26 $CHCl_3$), [lit.[55] $[\alpha_D]$ -16.9 (c 1.27, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ 0.00 (9H, s, Si(C*H*$_3$)$_3$), 0.97 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.25-1.45 (4H, m, C6'*H*$_2$Si + C2'*H*$_2$), 1.47 (3H, s, C4'C*H*$_3$), 1.94-2.01 (2H, quint. *J* = 6.8, C5*H*$_2$), 2.02-2.14 (3H, m, C1'*H*$_2$C3'*H*), 2.33-2.36 (2H, m, C4*H*$_2$), 2.41 (2H, app. t, *J* = 6.4, C6*H*$_2$), 5.19 (1H, td, *J* = 8.4, 0.4, C5'*H*), 6.68 (1H, t, *J* = 4.4, C3*H*). Data in agreement with that reported.[55]

(4a*S*, 5*R*, 6*S*, 8a*S*)-5,6-Dimethyl-8a-methylsulfanylmethyl-5-vinyl-octahydro-napthalene-1-one (86)[55]

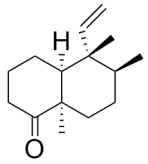


86

A solution of enone **85** (0.10 g, 0.36 mmol) and (chloromethyl) methyl sulfide (39 μL, 0.47 mmol, 1.3 equiv) in CH_2Cl_2 (3 mL) was added dropwise *via* cannula over 10 min to a solution of $TiCl_4$ (79 μL, 0.72 mmol, 2.0 equiv.), in CH_2Cl_2 (4 mL) at 0 °C under N_2. The reaction was stirred at 0 °C for 1 h before being poured onto H_2O (15 mL) and the layers separated. The aq. layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **86**. Purification by flash column chromatography (5% Et_2O/hexanes) gave sulfide (64 mg, 67%, lit.[55] 68%) as a colourless oil; R_f 0.15 (5% Et_2O/hexanes); $[\alpha]_D$ +83.6 (*c* 0.60, $CHCl_3$), [lit.[55] $[\alpha_D]$ +89.1 (*c* 1.41, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ 0.69 (3H, d, *J* = 6.8, CHC*H*$_3$), 0.81 (3H, s, CC*H*$_3$), 1.05-1.17 (1H, m, *Cy*), 1.19-1.28 (1H, m, *Cy*), 1.36-1.43 (2H, m, *Cy*), 1.72-1.79 (1H, m, *Cy*), 1.85-1.89 (1H, m, *Cy*), 1.92-2.10 (3H, m, *Cy*), 2.11 (3H, s, SC*H*$_3$), 2.26-2.35 (1H, m, *Cy*), 2.49 (1H, dt, *J* = 13.3, 4.0, *Cy*), 2.55-2.64 (1H, m, *Cy*), 2.79 (1H, d, *J* = 12.4, C*H*$_2$SCH$_3$), 3.07 (1H, d, *J* = 12.4, C*H*$_2$SCH$_3$), 4.93 (1H, dd, *J* = 17.6, 1.2,

CH=CH_{trans}H), 5.11 (1H, dd, *J* = 10.8, 1.2, H=CH_{cis}H), 5.41 (1H, dd, *J* = 17.6, 10.8, C*H*=CH_2). Data in agreement with that reported.[55]

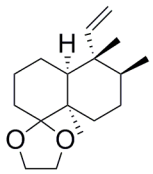
(4a*S*, 5*R*, 6*S*, 8a*R*)-5,6,8a-Trimethyl-5-vinyl-octahydro-naphthalen-1-one (197)[55]



197

A suspension of Raney nickel (0.70 g) in Me_2CO (5 mL) was stirred at reflux for 1 h before being cooled to rt and washed with THF (3 x 5 mL). The mixture was then suspended in THF (3 mL) to which sulfide **86** (90 mg, 0.34 mmol) in THF (2 mL) was added *via* cannula. The mixture was refluxed for 2 h before being cooled, filtered through celite® and washed with Et_2O (10 mL). The filtrate was then concentrated *in vacuo* to give crude **197**. Purification by flash column chromatography (10% Et_2O/hexanes) gave desulfurised *cis*-decalin **197** (63 mg, 85%, lit.[55] 96%) as a colourless oil; R_f 0.39 (10% Et_2O/hexanes); [α_D] +20.6 (*c* 0.55, $CHCl_3$), [lit.[55] [α_D] +38.6 (*c* 1.44, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ 0.70 (3H, d, *J* = 6.8, CHCH_3), 0.80 (3H, s, CCH_3), 0.97 (1H, td, *J* = 13.2, 5.6, *Cy*), 1.15-1.28 (1H, m, *Cy*), 1.30 (3H, s, CCH_3), 1.32-1.45 (2H, m, *Cy*), 1.67-1.81 (2H, m, *Cy*), 1.91-2.14 (3H, m, *Cy*), 2.19-2.25 (1H, m, *Cy*), 2.38 (1H, dt, *J* = 13.6, 3.2, *Cy*), 2.62-2.71 (1H, m, *Cy*), 4.93 (1H, dd, *J* = 17.5, 1.3, CH=CH_{trans}H), 5.10 (1H, dd, *J* = 10.8, 1.3, CH=CH_{cis}H), 5.42 (1H, dd, *J* = 17.5, 10.8, C*H*=CH_2). Data in agreement with that reported.[55]

(4a*R*, 5*R*, 6*R*, 8a*S*)-5,6,8a-Trimethyldecahydro-napthalene-1-spiro-2'-(1',3'-dioxolane (198)[55]

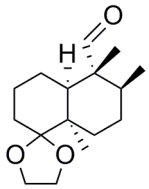


198

To a solution of decalin **197** (102 mg, 0.463 mmol), in toluene (15 mL) was added 1,2-dihydroxyethane (0.103 mL, 1.85 mmol, 4.0 equiv.) and CSA (5.50 mg, 23.2 μmol, 5 mol%) and the mixture was heated at reflux in Dean Stark apparatus for 48 h. The reaction was cooled, poured onto sat. aq. NH_4Cl (15 mL) and the layers

separated. The aq. layer was extracted with EtOAc (2 x 20 mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **198**. Purification by flash column chromatography (5% Et_2O/hexanes) gave ketal **198** (79.0 mg, 65%, lit.[55] 74%) as a pale yellow oil; R_f 0.66 (5% Et_2O/hexanes); [α_D] -3.2 (*c* 0.47, $CHCl_3$), [lit.[55] [α_D] -6.3 (*c* 1.42, $CHCl_3$)]; ^{1}H NMR (400 MHz) δ 0.75 (3H, d, *J* = 6.6, CHC*H*$_3$), 1.01 (1H, td, *J* = 13.2, *Cy*), 1.08 (3H, s, CC*H*$_3$), 1.15 (3H, s, CC*H*$_3$), 1.21-1.30 (2H, m, *Cy*), 1.41 (1H, dd, *J* = 6.6, 1.8, *Cy*), 1.46-1.61 (5H, m, *Cy*), 1.64 (1H, dd, *J* = 12.6, 4.9, *Cy*), 1.68-1.73 (1H, m, *Cy*), 2.05 (1H, dt, *J* = 14.4, 3.3, *Cy*), 3.90-3.97 (4H, m, OC*H*$_2$C*H*$_2$O), 4.93 (1H, dd, *J* = 17.4, 1.2, CH=C*H*$_{trans}$H), 5.02 (1H, dd, *J* = 10.8, 1.2, CH=C*H*$_{cis}$H), 5.44 (1H, dd, *J* = 17.4, 10.8, C*H*=CH_2). Data in agreement with that reported.[55]

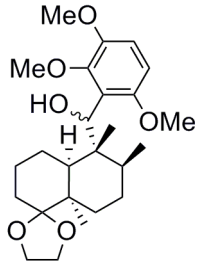
(4a*R*, 5*S*, 6*R*, 8a*S*)-9-Formyl-5,8,9-trimethyldecahydronapthalene-1-spiro-2'-(1'3'-dioxolane) (74)[55]



74

Through a solution of olefin **198** (0.22 g, 0.83 mmol) in CH_2Cl_2:MeOH (3:1, 8 mL) at –78 °C was bubbled ozone gas at a steady rate for 1 h. During this time the solution turned from colourless to pale blue. The solution was then flushed with nitrogen for 15 min before triphenylphosphine (0.26 g, 0.99 mmol, 1.2 equiv) was added and the mixture stirred and warmed to rt over 15 h. The mixture was concentrated *in vacuo* to give crude **74**. Purification *via* flash column chromatography (5-10% Et_2O/hexanes) gave aldehyde **74** (0.18 g, 79%, lit.[55] 92%) as a colourless oil; R_f 0.26 (10% Et_2O/hexanes); ^{1}H NMR (400 MHz) δ 0.92 (3H, d, *J* = 7.2, CHC*H*$_3$), 0.99 (3H, s, CC*H*$_3$), 1.00 (3H, s, CC*H*$_3$), 1.13-1.97 (1H, m, *Cy*), 1.31-1.52 (3H, m, *Cy*), 5.18-1.61 (3H, m, *Cy*), 1.68-1.74 (2H, m, *Cy*), 1.85-1.93 (2H, m, *Cy*), 2.01 (1H, br s, *Cy*), 3.89-3.97 (4H, m, OC*H*$_2$C*H*$_2$O), 9.31 (1H, s, C*H*O). Data in agreement with that reported.[55]

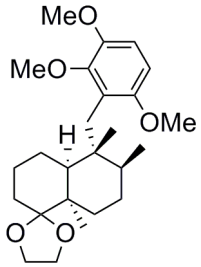
(4a*R*, 5*S*, 6*R*, 8a*S*)-5-{(2,3,6-Trimethoxyphenyl)[(*R*,*S*)-hydroxy]methyl}-5,6,8a-trimethyldecahydronapthalene-1-spiro-2'-(1',3'-dioxolane) (199)[55]



199

To a solution of 1,2,4-trimethoxybenzene (0.489 mL, 3.29 mmol, 5.0 equiv.) in THF (6 mL) under N_2 at 0 °C was added *n*-butyllithium (1.31 mL of a 2.5 M sol. in hexanes, 3.29 mmol, 5.0 equiv.) dropwise. The reaction was stirred at 0 °C for 30 min before aldehyde **74** (175 mg, 0.658 mmol) in THF (3 mL) was added dropwise *via* cannula. The reaction was stirred at 0 °C for a further 30 min before H_2O (20 mL) was added and the layers separated. The aq. layer was extracted with Et_2O (3 x 10 mL) and the combined organics washed with brine (10 mL) dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude alcohol **199**. Purification by flash column chromatography (25% EtOAc/hexanes) gave **199** (167 mg, 59%, lit.[55] 95%) as a colourless oil, as an inseparable 5:1 mixture of diastereoisomers; R_f 0.34 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz) (only peaks for major diastereoisomer quoted) δ 0.31 (3H, d, *J* = 6.4, CHC*H*$_3$), 0.84 (3H, s, CC*H*$_3$), 1.16-1.35 (4H, m, *Cy*), 1.38 (3H, s, CC*H*$_3$), 1.40-1.72 (5H, m, *Cy*), 1.83 (1H, dt, *J* = 12.8, 4.4, *Cy*), 2.19 (1H, sex, *J* = 6.8, *Cy*), 2.34 (1H, dd, *J* = 11.6, 4.4, *Cy*), 3.78 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 3.93-3.96 (4H, m, OC*H*$_2$C*H*$_2$O), 4.45 (1H, d, *J* = 11.2, CHO*H*), 5.22 (1H, d, *J* = 11.6, C*H*OH), 6.59 (1H, d, *J* = 9.0, Ar*H*), 6.77 (1H, d, *J* = 9.0, Ar*H*). Data in agreement with that reported.[55]

(4a*R*, 5*S*, 6*R*, 8a*S*)-5-[(2,3,6-Trimethoxyphenyl)methyl]-5,6,8a-trimethyldecahydronapthalene-1-spiro-2'-(1',3'-dioxolane) (200)[55]

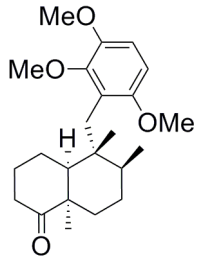


200

To a solution of alcohol **199** (167 mg, 0.385 mmol) in THF (12 mL), under N_2 at –78 °C was added NaHMDS (0.219 mL of a 1M sol. in THF, 1.16 mmol, 3.0 equiv.) dropwise. The reaction mixture was stirred at –78 °C for 30 min after which time CS_2 (0.152 mL, 2.50 mmol, 6.5 equiv.) was added and the mixture stirred and warmed to to –55 °C over 1 h. The reaction was then re-cooled to –78 °C and MeI (78.5 μL, 1.23 mmol, 3.2 equiv.) was added before being warmed to –55 °C over 1 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (10 mL) and allowed to warm to rt. The layers were separated and the aq. phase extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude xanthate. Purification by flash column chromatography (20% Et_2O/hexanes) gave (151 mg, 75%) as a yellow oil, as an inseparable unquantifiable mixture of diastereoisomers; R_f 0.38 (20% Et_2O/hexanes).

To a solution of xanthate (93.0 mg, 0.18 mmol) in toluene (6 mL) under Ar was added Bu_3SnH (0.20 mL, 0.72 mmol, 4.0 equiv.) and AIBN (2.9 mg, 18 μmol, 0.1 equiv.). The mixture was then degassed before being heated to reflux for 2 h. The reaction was then allowed to cool, filtered and concentrated *in vacuo* to give crude **200**. Purification by flash column chromatography (10% EtOAc/hexanes) gave **200** (72 mg, 97%, lit.[55] 92% over two steps from **199**) as a colourless oil; R_f 0.22 (10% EtOAc/hexanes); ^{1}H NMR (600 MHz) δ 0.87 (3H, d, *J* = 6.6, CHC*H*$_3$), 0.93 (3H, m, CC*H*$_3$), 1.15 (3H, s, CC*H*$_3$), 1.25-1.33 (3H, m, *Cy*), 1.36 (3H, app. sex, *J* = 4.8, *Cy*), 1.57-1.75 (5H, m, *Cy*), 1.85 (1H, dt, *J* = 14.4, 4.8, *Cy*), 2.61 (1H, d, *J* = 13.2, C*H*$_2$Ar), 2.91 (1H, d, *J* = 12.6, C*H*$_2$Ar), 3.73 (3H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$), 3.91-3.94 (4H, m, OC*H*$_2$C*H*$_2$O), 6.52 (1H, d, *J* = 9.0, Ar*H*), 6.72 (1H, d, *J* = 9.0, Ar*H*). Data in agreement with that reported.[55]

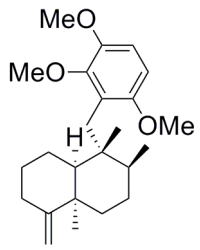
(4a*R*, 5*S*, 6*R*, 8a*S*)-5-[(2,3,6-Trimethoxyphenyl)methyl]-5,6,8a-trimethyldecahydronapthalen-1(2*H*)-one (201)[55]



201

To a solution of ketal **200** (72 mg, 0.17 mmol) in THF (4 mL) was added 1M HCl (4 mL) and the reaction stirred vigorously at rt for 4.5 h until TLC analysis showed complete consumption of starting material. The layers were separated and the aq. layer extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give ketone **201** (63 mg, 98%, lit.[55] 96%) as a colourless oil, which was used without further purification; R_f 0.32 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 0.82 (3H, s CC*H*$_3$), 0.93 (3H, d, *J* = 6.0, CHC*H*$_3$), 1.18 (3H, s, CC*H*$_3$), 1.24-1.40 (4H, m, *Cy*), 1.87-1.88 (1H, m, *Cy*), 1.93-1.97 (1H, m, *Cy*), 2.06-2.19 (5H, m, *Cy*), 2.59-2.65 (1H, m, *Cy*), 2.66 (1H, d, *J* = 13.6, C*H*$_2$Ar), 2.73 (1H, d, *J* = 13.2, C*H*$_2$Ar), 3.74 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 6.53 (1H, d, *J* = 8.8, Ar*H*), 6.75 (1H, d, *J* = 8.8, Ar*H*). Data in agreement with that reported.[55]

(4a*R*, 5*S*, 6*R*, 8a*S*)-5-[(2,3,6-Trimethoxyphenyl)methyl]-1-methylene-5,6,8a-trimethyldecahydronapthalene (202)[55]

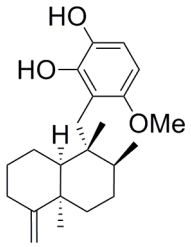


202

To a suspension of *t*-BuOK (297 mg, 2.67 mmol) in benzene (8.4 mL) at rt under Ar, was added $MePPh_3Br$ (955 mg, 2.67 mmol) and the resulting white suspension was heated at reflux for 1 h to give a yellow solution. After cooling to rt the solvent was removed under reduced pressure and the residue dried under vacuum for 30 min. The residue was dissolved in toluene (11 mL) and ketone **201** (50.0 mg, 0.134 mmol) in toluene (5.5 mL) was added *via* cannula. The reaction mixture was heated at reflux for 15 h before being cool to rt and diluted with H_2O (20 mL) and Et_2O (20 mL). The layers were separated and the aq. layer extracted with Et_2O (3 x 15 mL). The combined organics washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **202**. Purification by flash column chromatography (5% Et_2O/hexanes) afforded alkene **202** (37.4 mg, 76%, lit.[55] 75%) as a colourless oil; R_f 0.43 (5% Et_2O/hexanes); ^{1}H NMR (400 MHz) δ 0.87 (3H, d, *J* = 6.0, CHC*H*$_3$), 0.90 (3H, s, CC*H*$_3$), 1.06 (3H, s, CC*H*$_3$), 1.17-1.22 (1H, m, *Cy*), 1.27-1.32 (1H, m, *Cy*),

1.38-1.54 (3H, m, *Cy*), 1.59-1.65 (1H, m, *Cy*), 1.73-1.98 (3H, m, *Cy*), 2.01-2.06 (1H, m, *Cy*), 2.10 (1H, dd, *J* = 14.0, 5.2, *Cy*), 2.44 (1H, tdt, *J* = 13.6, 6.0, 2.0, *Cy*), 2.63 (1H, d, *J* = 13.2, C*H*$_2$Ar), 2.70 (1H, d, *J* = 13.2, C*H*$_2$Ar), 3.73 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 4.66 (1H, t, *J* = 1.6, C=C*H*$_2$), 4.70 (1H, t, *J* = 2.0, C=C*H*$_2$), 6.52 (1H, d, *J* = 8.9, Ar*H*), 6.74 (1H, d, *J* = 8.9, Ar*H*). Data in agreement with that reported.[55]

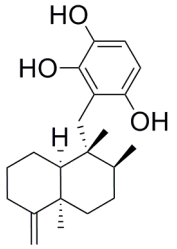
(4a*R*, 5*S*, 6*R*, 8a*S*)-4-Methoxy-3-(1,2,4a-trimethyl-5-methylene-decahydro-naphthalen-1-ylmethyl)-benzene-1,2-diol (203)[55]



203

To a solution of diphenylphosphine (0.139 mL, 0.806 mmol, 20 equiv.) in THF (4 mL) under N_2 at 0 °C was added *n*-butyllithium (0.386 mL of a 1.88 M sol. in hexanes, 0.726 mmol, 18 equiv.) dropwise. The reaction was stirred at rt for 30 min after which time arene **202** (15.0 mg, 40.3 μmol) in THF (2 mL) was added *via* cannula. The reaction mixture was heated at reflux for 15 h before being allowed to cool to rt and H_2O (10 mL) was added. The layers were separated and the aq. layer extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (10 mL), H_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10%-20% EtOAc/hexanes) afforded diol **203** (10.6 mg, 76% lit.[55] 71%) as a colourless oil; R_f 0.26 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 0.91 (3H, d, *J* = 6.0, CHC*H*$_3$), 0.92 (3H, s, CC*H*$_3$), 1.08 (3H, s, CC*H*$_3$), 1.18-1.30 (2H, m, *Cy*), 1.41-1.53 (2H, m, *Cy*), 1.56-1.67 (2H, m, *Cy*), 1.73-1.96 (2H, m, *Cy*), 1.98 (1H, app. dt, *J* = 3.2, *Cy*), 2.06-2.14 (2H, m, *Cy*), 2.44 (1H, m, *Cy*), 2.63 (1H, d, *J* = 14.0, C*H*$_2$Ar), 2.71 (1H, d, *J* = 14.0, C*H*$_2$Ar), 3.71 (3H, s, OC*H*$_3$), 4.68 (1H, m, C=C*H*$_2$), 4.71 (1H, m, C=C*H*$_2$), 6.27 (1H, d, *J* = 8.4, Ar*H*), 6.70 (1H, d, *J* = 8.4, Ar*H*). Data in agreement with that reported.[55]

(4a*R*, 5*S*, 6*R*, 8a*S*)-3-(1,2,4a-trimethyl-5-methylene-decahydro-naphthalen-1-ylmethyl)-benzene-1,2,4-triol (7)[55]



7

To a solution of diol **203** (10.6 mg, 28.5 μmol) in MeCN:H_2O (2:1, 2 mL) at 0 °C was added CAN (42.5 mg, 71.3 μmol, 2.5 equiv.) in MeCN:H_2O (2:1, 1 mL) fast dropwise to give a dark red solution. The solution was stirred for 30 min before warming to rt for a further 3 h. The reaction mixture was partitioned between H_2O (5 mL) and Et_2O (5 mL) and the layers separated. The aq. phase was extracted with Et_2O (2 x 5 mL) and the combined organics washed with brine (5 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo* to afford crude *p*-quinone **112**, R_f 0.68 (25% EtOAc/hexanes). The residue was dissolved in Et_2O (10 mL) and added to a solution of $Na_2S_2O_4$ (160 mg) in H_2O (10 mL). The mixture was shaken in a separating funnel for 10 min until TLC analysis showed complete consumption of starting material. The layers were separated and the organic layer washed with H_2O (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford crude **7** (5.0 mg, 53%, lit.[55] 58% from **203** after purification) as a yellow oil, which was used without purification; R_f 0.45 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 0.92 (3H, d, *J* = 6.0, CHC*H*$_3$), 0.95 (3H, s, CC*H*$_3$), 1.09 (3H, s, CC*H*$_3$), 1.20-1.32 (2H, m, *Cy*), 1.50-1.56 (3H, m, *Cy*), 1.60-1.74 (2H, m, *Cy*), 1.75-1.95 (3H, m, *Cy*), 2.09-2.12 (1H, m, *Cy*), 2.38-2.48 (1H, m, *Cy*), 2.65 (1H, d, *J* = 14.4, C*H*$_2$Ar), 2.70 (1H, d, *J* = 14.4, C*H*$_2$Ar), 4.68 (1H, m, C=C*H*$_2$), 4.71 (1H, m, C=C*H*$_2$), 6.20 (1H, d, *J* = 8.4, Ar*H*), 6.60 (1H, d, *J* = 8.8, Ar*H*). Data in agreement with that reported.[55]

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